

THE EFFECTS OF ENHANCED SENSORI-
MOTOR REHABILITATION ON INDICES OF
FUNCTIONAL PERFORMANCE IN
PATIENTS UNDERGOING TOTAL KNEE
REPLACEMENT

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Abstract of the thesis

The primary aim of this thesis addressed a knowledge gap regarding whether sensori-motor training (SMT) stimuli implemented early post-surgery are capable of targeting persisting sensori-motor and neuromuscular deficits in TKR patients' performance. Therefore, the effects of early enhanced sensori-motor training (ESMET) on self-reported and objective measures of physical function, sensori-motor, neuromuscular, and musculoskeletal performance capabilities of patients undergoing total knee replacement (TKR) were investigated.

In order to assess the effects of SMT on patients' functional mobility and sensori-motor function, as well as indirectly investigating the mechanism underpinning any observed effects, relevant outcome measures used in the literature were reviewed for their clinimetric properties. Indices of functional performance, as reflected by the Timed Up and Go Test (as primary outcome), balance-related performance, sensori-motor performance, neuromuscular performance, muscle size and knee ROM, as well as patient-reported measures (PROMs), were selected on the basis of their clinimetric utility to best reflect the outcome of the SMT intervention. A clinical survey of Greek physiotherapists' perspectives revealed that contemporary usual care management of TKR-related rehabilitation incorporated in the majority of cases home-based exercises with emphasis on knee ROM and muscle strengthening (Moutzouri et al, 2016b). A first systematic review including studies with IIc-IV level of evidence (Moutzouri et al, 2016c), revealed that patients undergoing TKR surgery experience persisting deficits in static and dynamic balance and incidence of falls remain within the pre-surgery levels. In parallel, a second systematic review evaluating preliminary effects of contemporary functional physiotherapy programmes being augmented by SMT in TKR clinical population, revealed statistically significant greater effects for balance performance but not for functional capabilities. However, the number of studies that had met inclusion criteria was small ($n = 5$) and the nature of their designs, which had been as pilot studies in the majority of cases, precluded conclusive findings.

Following preliminary investigations of reproducibility of measurement and related clinimetric characteristics of outcomes, the main aspect of the thesis reported on the findings of a novel randomised control trial (Moutzouri et al, 2017), in which the effects of a newly formulated time-matched sensori-motor exercise training programme [ESMET] was compared with those from a functional exercise training programme [FET] (representing the control condition and usual care practice, and which have been characterised by the findings of the aforementioned clinical survey) during rehabilitation following TKR. Participants ($n = 52$) were allocated to 12-week programmes of rehabilitation, initiated in the second week post-surgery, and assessed at pre-surgery (0 weeks), 8 weeks post-surgery, and at 14 weeks post-surgery on outcomes which included indices of self-reported and objective measures of physical function, sensori-motor, neuromuscular, and musculoskeletal performance capabilities. The findings revealed significant advantages for the new sensori-motor focused rehabilitation on several outcomes (relative effect size range at 14 weeks post-surgery ~ 0.5 to 2.1), including a significant group by time interaction ($F_{(1.7, 82.5)}_{GG} = 11.0$; $p < 0.005$) for the study's primary outcome (Timed Up and Go Test), favouring ESMET over FET by $\sim 35\%$. However, the study's findings need to be interpreted with caution due to the single-blind nature of the study.

Key words: total knee replacement; knee osteoarthritis, Rehabilitation; Balance; sensori-motor training

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Dedication

I dedicate this work to my beloved parents!

The sacrifices support and care you provided me can never be paid back.

However, I will live to make you both proud of me.

I also want to dedicate this thesis to my loving husband and baby son, whose smile gave me courage and motive.

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Abbreviations

10WT 10 minute Walk Test
2MWT 2 minute Walk Test
30SCT 30 Second Chair Stand Test
ABC-S Activities-specific Balance Confidence Scale
ACL Anterior Cruciate Ligament
ADL Activities of Daily Living
ANCOVA Analysis of Covariance
ANOVA Analysis of Variance
APSI Anteroposterior Stability Index
BSS Biodex Stability System
CASP Critical Appraisal Skills Programme
CI Confidence Interval
CNS Central Nervous System
COM Centre of mass
CONSORT Consolidated Standards of Reporting Trials
COP Centre of pressure
CSA Cross-Sectional Area
CV Coefficient of Variation
EMD electromechanical delay
EMG Electromyography
ESMET Enhanced Sensori-motor exercise Training
FET Functional exercise therapy
FRT Functional Reach Test
ICC Intra-class Correlation Coefficient
JPE Joint Position Error
JPS joint position sense
KOOS Knee injury and Osteoarthritis Outcome Score
KOS-ADL Knee outcome survey- Activities of Daily Living Scale
KSS Knee Society Score
LCL Lateral Collateral Ligament
LEFS Lower Extremity Functional Scale
LOS Length of Stay
MCID Minimally Clinically Important Difference
MCL Medial Collateral Ligament

MDC Minimal Detectable Change
MIS Minimally invasive Surgery
MLSI Mediolateral Stability Index
MVMA Maximal Voluntary Muscle Activation
MVIC Maximal Voluntary isometric contraction
NHS National Health Service
NMES neuromuscular electrical stimulation
NPRS Numerical rating scale
OA Osteoarthritis
OSI Overall Stability Index
PCL Posterior Cruciate Ligament
PEDro Physiotherapy Evidence Database rating scale
PF Peak force
PPA Physiological Profile Assessment
PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL Quality of Life
RCT Randomised Control Trial
RF Rectus Femoris
RFD Rate of Force Development
RMS Root mean square
ROM Range of motion
SD Standard Deviation
SEC series elastic component
SEM Standard Error of Measurement
SF-12 Short Form Health Questionnaire 12
SF- 36 Short Form Health Questionnaire 36
SLSB Single limb standing balance
SLST Single Limb Standing Test
SMP Sensori-motor performance
SMT Sensori-motor training
TJR Total Joint Replacement
TKR Total Knee Replacement
THR Total Hip Replacement
TTDPM Threshold to Detect Passive Motion
TUG Timed Up and Go

UKR Unilateral Knee Replacement

US Ultrasound

VAS Visual Analogue Scale

WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

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Chapter 1

Introduction

1.0 Introduction

As early as 1928 the New York Heart Association recognised the importance of evaluating the effects of disease on functional performance. Guralnik *et al* (1989) suggested that *'by understanding functional capacities of patients, caregivers are better able to judge disease severity, the impact of multiple morbidity (which is common in the elderly) and the need for rehabilitation services'*. Independence in performing activities of daily living (ADL) provides the patient with the foundation for developing good quality of life (QoL) parameters and satisfactory performance according to his/her personal demands.

The issues surrounding functional performance are considered critical in chronic pathologies such as osteoarthritis (OA) of the knee (Dunlop *et al*, 2011). Osteoarthritis, also called degenerative joint disease, is the most common systemic disorder in synovial joints such as the knee, and is characterised by loss of articular cartilage (Woolf & Pfleger, 2003). There is a general consensus that OA is a mechanically driven joint disease, which is evident in people who have had injury or surgery and the joint structure is affected so that the joint is less stable (Roos, 2015). Patients with knee OA report pain and difficulty with functional activities such as prolonged sitting, ascending and descending stairs, walking, squatting, kneeling, rising from a chair and getting in and out of a car. Factors found to place individuals with knee OA at greater risk of poor functional performance include the local factors of laxity (knee instability) and proprioceptive inaccuracy, as well as age, BMI, and knee pain intensity (Fitzgerald *et al*, 2004; Sharma *et al*, 2003; Schmittet *al*, 2008). On the contrary, muscle strength, psychosocial factors, mental health, self-efficacy, social support, and aerobic physical activity levels influence functional performance positively (Sharma *et al*, 2003). The identification of these factors provides possible targets for rehabilitative and self-management strategies to prevent disability.

Proprioception is the awareness of the body in space. It is the use of joint position sense and joint motion sense to respond to stresses placed upon the body by alteration of posture and movement (Houglum, 2001). Practically, it is the ability of the body to use position sense and respond (consciously or unconsciously) to stresses imposed on the body by altering posture and movement. Proprioception or kinaesthesia are amongst the synonymous terms used in contemporary literature to describe the body's capability to control movement, with sensori-motor performance

(SMP), being more recently used as the preferred term (Lephart & Fu, 2000). The term “sensori-motor performance” describes the process by which the responses from several types of neural receptors arising from internal peripheral areas of the body are integrated to produce both sensory awareness postural control, joint stability and commensurate motor responses (Riemann & Lephart, 2002). Sensori-motor performance (SMP) is considered fundamental to the enhanced control of neuromuscular performance, functionality, and biomechanically ordered, efficient and effective movements. Diminished SMP is identified as a contributing factor to the loss of balance control and, resulting therefore, in falls within the elderly.

Knee OA has been considered an established risk factor for falls among older people (Guideline for the prevention of falls in older persons). Research suggests that diminished SMP may initiate or even accelerate the degenerative process of OA (Barrack *et al*, 1983; Barret *et al*, 1991). Severe degenerative processes in the OA knee cause debilitating pain, loss of postural control, altered gait patterns, functional deprivation and therefore diminished QoL, and are often requiring joint arthroplasty surgery, known as total knee replacement (TKR). Resurfacing the articular surfaces and retensioning the capsuloligamentous tissues re-establishes the capability for maintaining balance (mechanical stability) in the joint. Mechanical stability is critical for the success of TKR. Therefore, re-establishing SMP, dynamic stability forces, and joint alignment maximises the prosthesis longevity. In the progression of OA, sensori-motor skills including proprioception, static and dynamic balance, and neuromuscular control are known to degrade in response to pain avoidance and advancing inactivity (Bitterly, 2011; Cameraman, 2011). These sensori-motor deficiencies and muscle weaknesses typically manifest as modified movement patterns and have been shown to persist even after joint replacement (Davidson, 2013, Dwyer 2013). For instance, Thewlis *et al* (2014) observed persistent asymmetric load distribution in TKR patients six months after surgery and Levanter *et al* (2012) described proprioceptive deficits that remained for at least twelve months following TKR. A recent history of falls is common in individuals who had TKR, and ~45 % of patients fall again in the year following surgery (Levinger *et al*, 2012). Only 66 % of TKR patients report their knee to feel ‘normal’ versus 87 % of patients following total hip replacement (THR) (Nunley *et al*, 2011), with the reported incidence of residual symptoms and functional problems ranging from 33 % to 54 % in TKR (Nam *et al*, 2013). The exact reasons for this large discrepancy in outcomes

between TKR and THR remain unclear. However, what remains most significant is that there is a great margin for improving outcomes and patient satisfaction following TKR. Contemporary usual care programmes focus on knee ROM, muscle strengthening and functional exercises achieving up to 25 % in performance-based functional outcomes (Timed Up and Go Test) one year post-surgery (Lowe *et al*, 2007; Mizner *et al*, 2011; Pozzi *et al*, 2013). However, the extent of recovery has not fully reached patients' expectations (Choi & Yong, 2016; Kim *et al*, 2009; Nillsdotter *et al*, 2009). Accelerated protocols of rehabilitation have primarily focused on enhancing the peri-operative care of patients, by implementing pain management, early mobilisation and patient education (Isaac *et al*, 2005; Minns-Lowe *et al*, 2007; Robertson *et al*, 2015). These protocols have shown improved patient outcomes and reduced length of hospital stay, however mid-term functional and falls incidence have not been recorded. A reduction in fear of falling and pain, as well as improvements in function for the surgical group have been reported, however, the number of falls experienced following TKR surgery remained high. The follow-up periods of the above studies are up to one year (Levinger *et al*, 2012; Swinkels *et al*, 2009).

The control of knee sensori-motor performance seems to be modifiable after injuries, and in knee OA following specific exercise therapeutic approaches (Knoop *et al*, 2011; Mat *et al*, 2014). Therefore, a critical goal for the patient undergoing TKR is to follow a therapeutic approach which ensures physical protection of relevant challenges in order to optimally reduce the difficulties and a risk of falling occurring during ADL. Therapeutic management of deficits in SMP and neuromuscular control is a concept that has received increased attention in the past several years. Similarly, enhancement of specific motor skills that require neuromuscular coordination, agility and balance have been acknowledged as essential components of rehabilitation, as distinct from isolated one-plane movement patterns of muscular strengthening. Several investigators have noticed that muscle strengthening in isolation cannot control functional joint instability after knee or ankle injury (Richie, 2001, Hewett *et al*, 2002). The desired responses after injury translate to three therapeutic goals: enhancement of a) joint position sense and kinaesthesia b) dynamic joint stabilisation and c) postural control and balance. Therefore, heightened awareness of proprioceptive deficits associated with (common sports injuries and OA) has led to a greater focus on specific sensori-

motor training (SMT) as a component of rehabilitation, and which has been acknowledged as being especially important for safe return to activities (Fitzgerald *et al*, 2002; Roos & Arden, 2016). Accumulating evidence indicates that functional rehabilitation is inadequate unless specific mechanisms associated with proprioception and neuromuscular control, are addressed.

The component of rehabilitation designed to restore these mechanisms, considering the integrated neuroanatomy and neurophysiology of the sensory and motor systems, is described as sensori-motor training (SMT). Alterations of somatosensory, visual or vestibular input are commonly used to challenge a particular facet of the sensori-motor mechanism. Although sophisticated equipment is available, clinicians often use inexpensive wobble boards, foam mats and similar devices that permit perturbation and therefore stimulation of musculotendinous and joint receptors. Sensori-motor training was traditionally used in the final stage of functional rehabilitation, however, it is now acknowledged as a mode of training included in all of phases of rehabilitation, progressing from simpler to more complex motor tasks. Incorporation of locomotor skills within SMT is commonly used to utilise input from all aspects of the sensory system to promote neuromuscular responses at all hierarchical levels of motor control.

Data from 27,000 individuals found that neuromuscular and SMT programmes are successful in preventing 50% of major knee injuries during sport, which indicates that primary prevention of knee OA is possible (Bennel *et al*, 2008; Gagnier *et al*, 2013; Roos, 2005; Roos *et al*, 2011). Knee injury prevention, rehabilitation after knee injuries, targeted exercise therapy, dynamic joint stability, muscle function and maintaining body weight may prevent OA initiation and progression in young adults (Roos, 2005). This type of training is based on biomechanical principles that target the sensori motor system, stabilise the joint while in motion and improve patients' trust in their knee. This active approach to the sensori-motor system improves biomechanics, which may alter contact stress and therefore delay or prevent the onset of OA. Experts have highlighted the importance of mechanical loading for maintaining a healthy cartilage (Gomiero *et al*, 2011). While joint-related factors are likely important for both pain and disability, there is now extensive evidence that, similar to other chronic pain conditions, OA is associated with a range of neuroplastic changes in the central nervous system that may contribute to both pain

and motor impairments (Dimitroulas *et al*, 2014). These findings suggest that a substantial amount of the variance in both OA-related pain and disability may occur due to brain-related, rather than simply joint-related impairments. In terms of potential mechanism, SMT has been found recently to induce structural plasticity changes in brain regions of the cortical cortex (visual, vestibular) known to control spatial orienting and self-motion perception (Rogge *et al*, 2018).

Sensori-motor training has been shown to produce positive effects on the response of hip OA and total hip replacement (THR) patients to sudden displacements (Lin, 2009), improve walking time and reduce knee reposition error in knee OA patients compared to strength training (Boeer, 2010). Despite evidence that a full recovery of sensori-motor function is unlikely to occur within twelve months of TKR (Levanter *et al*, 2012), there is emerging evidence that sensori-motor function can be improved through dedicated SMT. Along with muscular strengthening, joint flexibility training, and pain management, SMT has now become an integral part of rehabilitation guidelines following THR and TKR. However, evidence-based recommendations for SMT, particularly in post-operative rehabilitation programmes, are currently lacking. Current guidelines are based mainly on anecdotal evidence and practical experience. Empirical evidence regarding the optimal SMT dose and the effects of training volume, frequency, duration, and intensity is still to be explored.

Summarising evidence, patients undergoing TKR, still face challenges with the ADL and are at risk of falls as early as a week post-surgery when discharged at home. Thus, rehabilitation needs to be targeted to address these deficits as early as possible within an environment that can pragmatically ensure patient' safety and autonomy. Therefore, the innovation lately within post-operative rehabilitation is the addition of sensori-motor elements in exercises in the usual care functional training (Gstoettner *et al*, 2011; Liao *et al*, 2013; Piva *et al*, 2010). This has been reported as having the potential for improving stability performance compared to conventional approaches and so, potentially favours the use of this type of 'combined' intervention, involving greater emphasis on conditioning sensori-motor performance. However, the problem is that so far studies that implemented SMT programmes in patients undergoing TKR have used it as an additional component increasing the duration of the usual care. As a result, the effect of SMT on patients' functional performance and the mode that should be implemented is not yet clear. Many

countries have health care systems focused on value-based care, which are systems focused on understanding the cost drivers, implementing high-value therapies, and improving methods and/or techniques to assess knee instability and rehabilitation therapies that could potentially reduce the health care costs associated with the knee. Therefore, the components, the environment and the timeline associated with rehabilitation post-TKR remain crucial areas that need to be addressed.

1.2 Aims

Statement of the problem

Having discussed the concept of SMT and the residual deficits of TKR patients, this thesis primarily aims to investigate the effects of the relatively novel approach of enhanced sensori-motor therapy conditioning on the functional, sensori-motor, neuromuscular, musculoskeletal and psycho-physiological performance of patients following TKR. Enhanced sensori-motor exercise training (ESMET) may be defined as a form of rehabilitative training which is highly focused on improving SMP, but which is time-matched with usual care. It is also implemented earlier-than-usual (according to relevant literature) but nevertheless, is considered to produce safe and functionally-relevant recovery. The primary aim of the thesis ultimately will be to evaluate the efficacy to improve functionality and physical performance capabilities of a novel formulation of post-surgery rehabilitation for patients undergoing TKR involving an increased emphasis on sensori-motor training (Chapter 8).

These thesis aims pose the following questions (Table 1.1).

Table 1.1 Research questions posed.

Thesis Questions
1. Is there evidence that the ESMET programme has an effect (compared to control) on the primary outcome measure of functional performance (TUG) within a TKR clinical population?
2. Is there evidence that the ESMET programme has an effect (compared to control) on sensori-motor function, neuromuscular and musculoskeletal performance within a TKR clinical population?
3. Is there evidence that the ESMET programme has an effect (compared to control) on pain and self-reported measures of function and psycho-physiological performance within a TKR clinical population?

ESMET: enhanced sensori-motor exercise training group; TUG: timed up and Go Test; TKR: Total Knee Replacement.

In order to achieve this primary aim, the following subsidiary aims were considered (Figure 1.1):

- To set the background of the study (Chapter 2) by defining the key conceptual terms of the thesis, analysing OA patients' impairments and identifying the gaps in the literature regarding rehabilitation strategies for OA patients undergoing TKR;
- To assess the clinimetric properties of outcomes reflecting functional, sensori-motor, neuromuscular and musculoskeletal performance as well as related patient-reported measures in the field of TKR-related literature, so as to select the ones that will be used in the main study (Chapter 3);
- To describe current standard (usual) care for patients undergoing TKR through a clinical survey in Greece (Chapter 4; Moutzouri et al, 2016b). Following the findings of that survey and the findings from relevant international literature to establish what might be considered as usual care practice. This information will be used to inform the timeline and environment for the thesis' main study;
- To identify the extent of the effects of TKR on balance and incidence of falls in patients with knee osteoarthritis following total knee replacement (Chapter 5; Moutzouri *et al*, 2016c), by critically reviewing the available literature (performed in September 2014). This study was performed in parallel to the main RCT study to facilitate understanding of the mechanisms associated with the recovery of the systems that control balance and to identify any balance-related residual problems after TKR. In this way, any effects observed from SMT from the analysis of results of the main RCT can be artificially separated from the effects of TKR surgery;
- To investigate the effects of SMT on balance and functional performance in patients following TKR, through a systematic review of the literature (Chapter 6; Moutzouri *et al*, 2016a) (performed in December 2014). The scientific evidence from this study, also performed almost in parallel to the main RCT study, may ultimately help to criticise and/or confirm the design of an integrated enhanced exercise

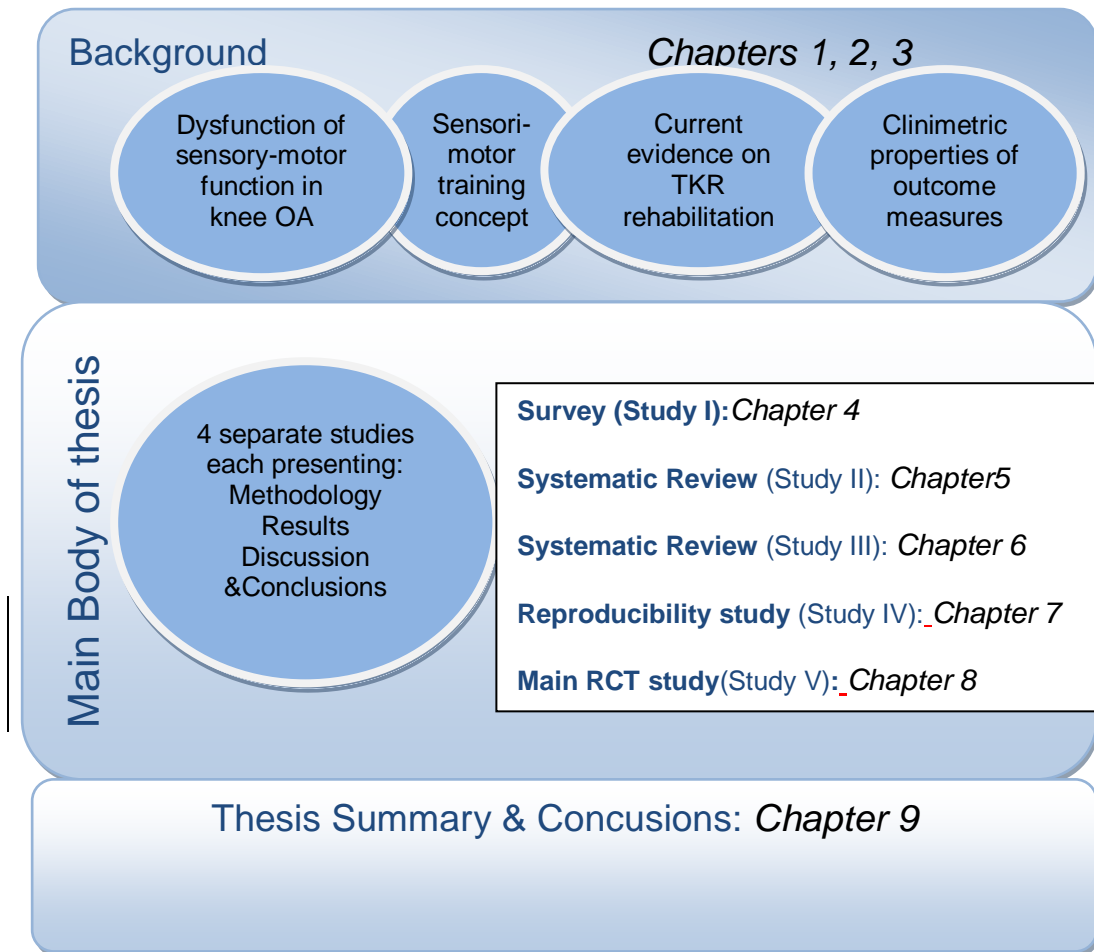
training programme. Strengths and limitations of current evidence will be evaluated. Questions that will seek to be answered include, which components of SMT are needed to be added to the usual care (functional exercise training), what is the appropriate timing of initiation, and what is the sufficient volume of exercise to elicit responses;

□ To assess the reproducibility, stability and single-measurement reliability of the selected indices of functional, sensori-motor, neuromuscular and musculoskeletal performance of the knee at all assessment occasions (Chapter 7), in order to ensure clinically useful interpretation of the findings of the main study;

□ In parallel chronologically with the systematic reviews analyses, the main thesis RCT study was designed (performed from May 2012 to May 2014) to evaluate the clinical effectiveness of usual care practice (functional exercise training) integrated with novel sensori-motor elements that might potentially enhance the clinical care of patients and address persisting deficits that challenge patients' ADL, in indices of balance-related and sensori-motor performance as well as self-reported indices of function and quality of life, (Moutzouri *et al*, 2017). Moreover, in order to investigate indirectly underlying mechanisms of SMT, relationships amongst indices of functional, balance-related, sensori-motor, neuromuscular and musculoskeletal performance of patients undergoing TKR will be examined (Chapter 8, Moutzouri *et al*, 2019 accepted subjected to minor corrections);

□ A thesis summary and conclusion that draws together the findings of the various studies and will discuss how the thesis' aims have been addressed and what future work is recommended (Chapter 9).

Figure 1.1 Structure of the thesis.



Chapter 2

Background

2. Background

The conceptual model of the human musculoskeletal system depicts an interactive action of the bones, muscles, ligaments, tendons and joints (Qun *et al*, 2005). The muscular part of this system is associated with producing purposeful movements following directives from the Central Nervous System (CNS), while the osseous part is regarded as protecting the internal structures of the human body, alongside with the provision of a stable framework for the former movements (Farley *et al*, 2012).

2.1 Functional anatomy and stability of the knee joint

The knee joint is one of the largest and most complex joints of the body, so understanding of its functional anatomy is necessary to determine physiological and pathological function. The knee joint is a trochoginglymus (i.e. a pivotal hinge joint). There are three separate joint surface pairs within the knee. They are the patello-femoral, the medial tibio-femoral and the lateral tibio-femoral joints. The mechanical axis of the lower limb crosses the center of the knee joint, which leads to near equal loading of the medial and lateral part of the knee. Congenital and acquired abnormalities may lead to significant walking impairments, or early degenerative alterations (i.e. osteoarthritis) that may affect the whole joint or different compartments. The menisci add to the loading surfaces of the joints, and ensure congruency in the joint. Accordingly, they are mobile and they move passively when the knee is flexed or rotated. When the knee is bent the femoral condyles slide and roll along the tibial joint surfaces. Knee joint motion is rather complicated due to the coupling of flexion/extension with internal/external rotation and translation of the tibia relative to the femur (Blankevoort *et al*, 1990; Wolf, 2014).

The process of maintaining functional joint stability in various positions is accomplished through a complementary relationship between active (musculature of the knee) and passive components (strong network of ligaments). Stability of the knee joint is also maintained by the shape of the condyles and menisci in combination with the passive supporting structures. These are the four major ligaments, the anterior cruciate ligament (ACL), the posterior cruciate ligament (PCL), the medial collateral ligament (MCL), and the lateral collateral ligament (LCL). Significant contributions are also made by the postero-medial and postero-lateral capsular components and the iliotibial tract. Figure 2.1 illustrates the

anatomical structures of the knee joint. Co-activation of the antagonist muscles of the knee joint provide substantial basis for joint stability which is further synergistic to that provided by the ligaments. For example, when the knee extends, the ACL is gradually loaded and simultaneously the hamstrings provide synergistic action to that of the ACL

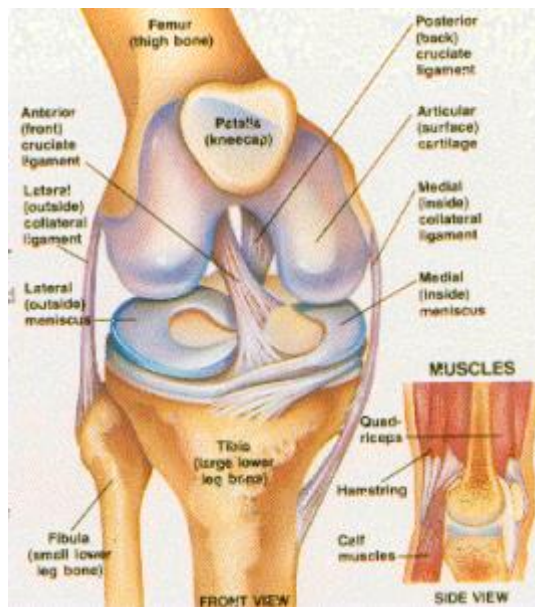


Figure 2.1 Illustration of the anatomical components maintaining stability of the knee joint. (adapted from <http://chrissophysio.com/wpcontent/uploads/2013/12/knee-anatomy-269x300.png>).

Functional knee joint stability has been defined as the situation in which the knee has adequate stability to perform a functional activity (Garret *et al*, 1992). Functional joint stability encompasses a more focal ability of the body to ensure the appropriate joint stiffness in order to avoid tissue injury (Rienmann *et al*, 2002). Functional knee instability on the other hand is a symptom that refers to the sensation of buckling, slippage, or giving way of the knee during functional activities (Noyes *et al*, 1989). Therefore, functional joint stability is a complex physiological process, determined by the inter-action of passive and dynamic restraints. In the absence of mechanical stability, compensatory mechanisms develop to provide the required stability. Motor control and muscle stiffness undergo constant regulation to determine the load and stability of the joint. Therefore, the importance of muscle coordination for the enhancement of functional stability is highlighted.

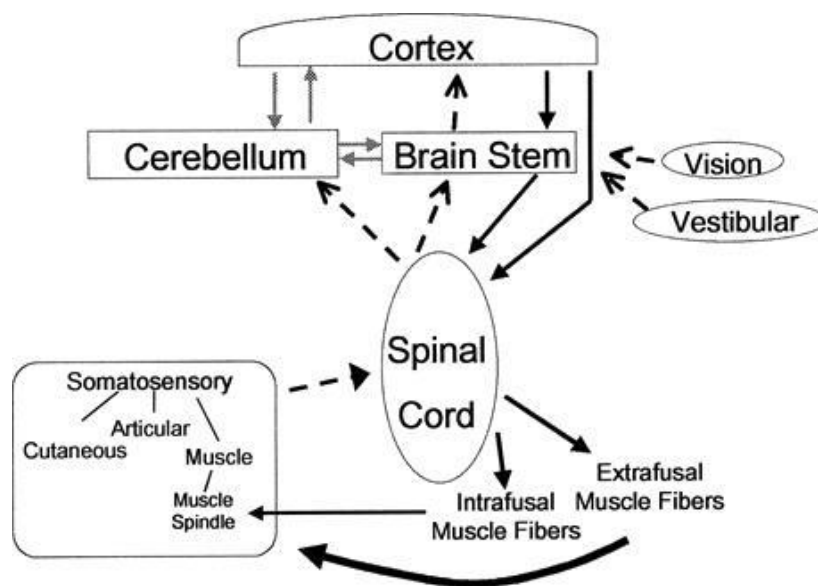
Efficient movement execution and dynamic stabilisation of joints requires an adequate capability for both neuromechanical and sensori-motor performance (Lephart & Fu, 2000). The latter is partly dependent upon afferent information

directed from proprioceptors located within the contractile and non-contractile elements of the muscle-joint system. A premise underpinning the conceptual model for knee joint stability is that SMP is fundamentally linked with injury prevention and is one of the most important mechanisms of joint protection.

2.2 The “sensori-motor system” of the knee joint

The term *sensori-motor system* was adopted by the participants of the 1997 Foundation of Sports Medicine Education and Research workshop to describe the sensory, motor, and central integration and processing components involved in maintaining joint homeostasis during bodily movements (functional joint stability) (Riemann & Lephart, 2002) (Figure 2.2). The term sensori-motor has been adopted to represent the composite of the physiological systems of the complex neuro-sensory and neuromuscular process, which have been frequently simplified and inappropriately described as *proprioception* (Lephart & Fu, 2000). The sensori-motor system, a subcomponent of the comprehensive motor control system of the body, is extremely complex.

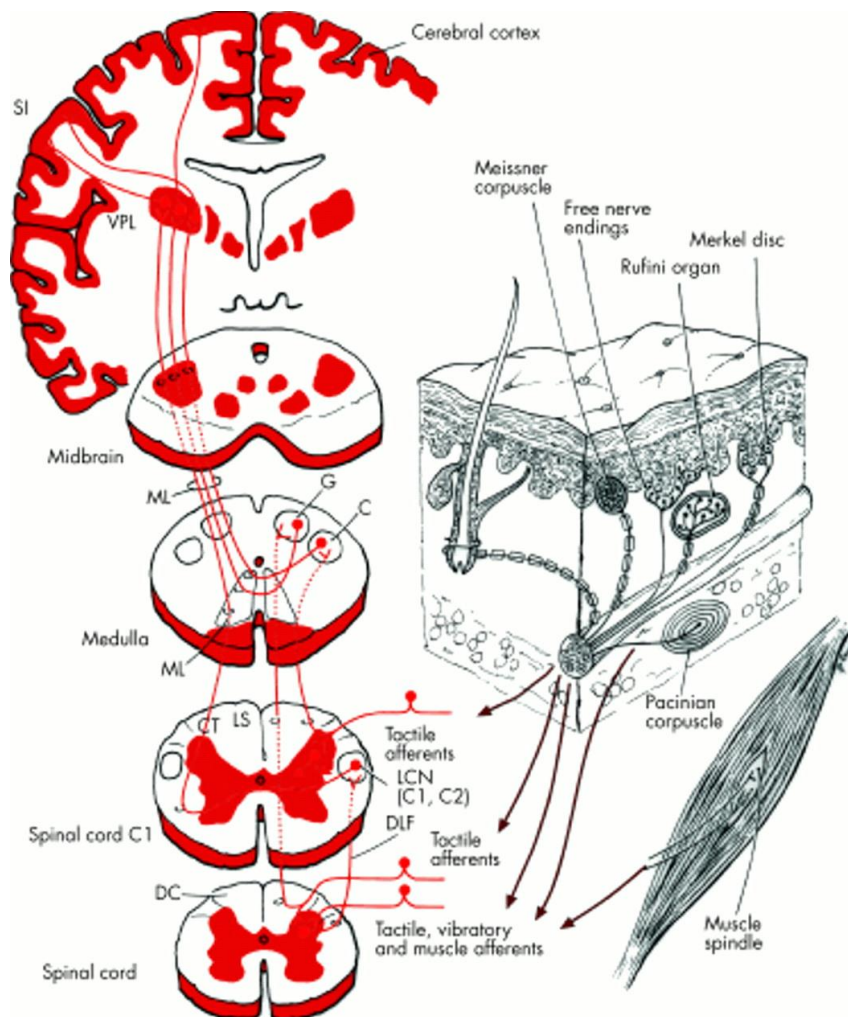
Figure 2.2 The sensori-motor system (adapted from Riemann & Lephart, 2002).



Proprioception, one of the most important regulatory mechanisms, predominates as the most misused term of the sensori-motor system. Proprioception acuity is defined as “a person’s ability to be aware of the movement and position of a limb by means of sensory information from the nerve receptors in the capsule, ligaments, tendons

and muscles” (Sherrington, 1906). Proprioception consists of the sense of position and movement of the limbs and body in the absence of vision (Figure 2.3). Proprioception includes two components, the sense of stationary position of the limbs (limb position sense) and the sense of limb movement (kinaesthesia). Proprioception, body-awareness or sensori-motor performance are labeling terms that have been used synonymously in the contemporary literature to describe capabilities that are considered fundamental to the enhanced control of neuromuscular performance, functionality, and biomechanically ordered, efficient and effective movements. Sensori-motor performance has become the preferred term (Lephart and Fu, 2000).

Figure 2.3 Diagram of the peripheral receptors and central pathways mediating joint position sense, vibration sense, and tactile sensation. The lower diagram on the right illustrates the receptors principally responsible for position sense, which are muscle spindle primary and secondary afferents (adapted from Gillman, 2002).



The term “sensori-motor performance” describes the process by which the responses from several types of neural receptors arising from internal peripheral areas of the body are integrated to produce both sensory awareness postural control, joint stability and commensurate motor responses (Riemann & Lephart, 2002). In this process, the sensory stimulus is transformed into a neural signal and transmitted via an afferent pathway to the central nervous system where this signal is then integrated and calibrated into an appropriate motor response for locomotion and functional joint stability. Sensori-motor performance information originates within the tendon, ligament, joint capsule, skin and muscle surrounding the knee. Palmar (1944) introduced the theory whereby the ligaments within the knee supply the CNS with the input that makes neuromuscular control of the knee joints possible. Cohen (1955) subsequently suggested that the knee joint capsule originated protective afferent input to CNS making the idea of ‘arthrokinetic reflex’ more familiar to the scientific community.

Receptors are specialised cells or subcellular structures that change their properties in response to specific stimuli (sources of energy). Thus, different receptor systems enable humans to differentiate sources of energy such as light, sound and mechanical energy (Latash, 2008). The obvious function of receptors is to make information about specific stimuli available to other neurons within the CNS. There are three types of receptors: *interceptors* that transduce information from within the body, *exteroceptors* that transduce information from the environment and finally the proprioceptors that transduce information about the relative configuration of the body segments (Latash, 2008). All the previously mentioned receptors generate a neural reflex that is defined as involuntary action in response to a stimulus applied in the periphery and is transmitted to CNS, in the brain or the spinal cord providing stability and stiffness to the knee joint (Beard, 1993). It was demonstrated that when the receptors were sensing a mechanical stress within the ACL, feedback travelled through the CNS to result in an immediate contraction of the knee musculature for the optimal protection of the joint (Solomonow *et al*, 1987). Thereby, reduced proprioception acuity could mean less information to the CNS, less efficient delivery of relevant information to the CNS, delayed information to the CNS, reduced sensibility of receptors, or that a combination of any of the latter contributing to less efficient or less accurate/precise information on which to deliver responses.

Several types of sensory receptors are found in the tissues of the knee joint. Amongst those are pacini corpuscles, Golgi joint receptors, Golgi tendon receptors, Ruffini endings, muscle spindles and bare nerve endings (Solomonow & Krogsgaard, 2001).

Pacinian corpuscles

They are found in the deeper layer of the joint capsule, cruciate and collateral ligaments, menisci and fat pad. They are silent in static conditions but are very sensitive to mechanical stress, initiation and termination of motion, acceleration and deceleration; therefore act as pure dynamic mechanoreceptors that adapt rapidly.

Golgi receptors

Golgi receptors embedded in the knee joint are known to signal the angle of the joint while Golgi receptors in the muscle's tendons, signal the force developed by the muscle. They provide the CNS with feedback regarding muscle tension.

Ruffini endings

They are found in the collateral and cruciate ligaments, capsule and menisci. They signal both static and dynamic conditions such as joint angle, intra-articular pressure, and strains and unlike Pacinian receptors adapt slowly.

Muscle spindles

They are found in muscles crossing the joint and are sensitive to muscle elongation, velocity and acceleration. There are different types of intrafusal fibres: some are mainly sensitive to changes in muscle length whereas others are more sensitive to the rate of change of muscle length. The spindle projection ascends to the spinal cord and terminates to the cerebellum.

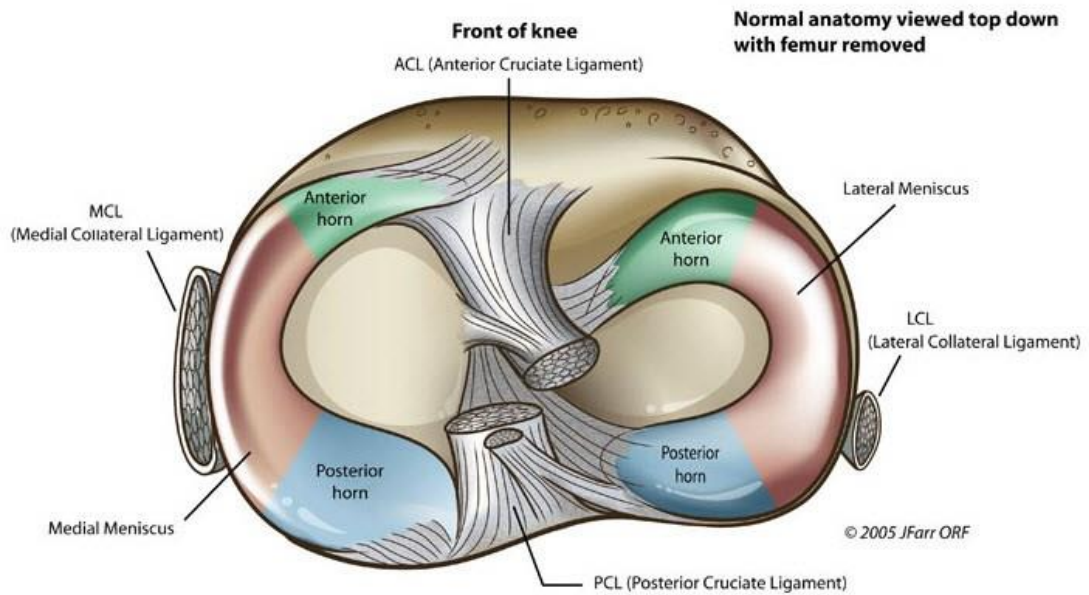
Free nerve endings

They respond to stimuli excessive to what a tissue is normally subjected and indicate strongly nociceptive information (pain). They are richly found in the articular surfaces and ligaments.

The knee joint has a wide range of movements that are supported by the surrounding ligaments, tendons and muscles (Figure 2.4).The capsuloligamentous

system is comprised of the joint capsule, medial and lateral collateral ligaments, anterior and posterior cruciate ligaments, popliteus tendon, hamstrings tendons and the menisci. The proprioceptive inputs from these surrounding structures are important for knee stability. It has been proposed that impaired proprioceptive accuracy in the knee is a local factor related to the onset and progression of radiographic knee osteoarthritis (Felson *et al*, 2009). Kennedy *et al* (1982) described mechanoreceptors and nerve fibres in the posterior cruciate ligament (PCL), anterior cruciate ligament (ACL), meniscus and capsular structures. Cabuk *et al* (2016) in a recent cadaveric study, aimed to determine histologically the density and distribution of mechanoreceptors, and develop a neuroanatomical map of the ligaments and tendons around the knee that are important for knee stability. It was found that free nerve endings were the most common type of mechanoreceptor in the knee, followed by Ruffini corpuscles and Golgi-like endings. Mechanoreceptors were primarily located in the cruciate ligaments and lateral structures rather than the medial structures. Most of them were also located near the bone insertions. Mechanoreceptors located close to the bone insertions of ligaments could communicate responses to minor changes in tension rapidly, because ligaments are more resistant to strain in regions close to their insertion sites (Solomonow, 2006). Ruffini endings were also found more frequently in the lateral complex and the cruciate ligaments than in the medial complex and the patellar tendon. Because the tibial plateau is concave on the medial side and convex on the lateral side, the lateral femoral condyle travels a greater distance than the medial side during flexion and extension (Amiri *et al*, 2006). Therefore, although the ligaments and tendons of the lateral complex are highly mobile, the medial tibial plateau and the medial side structures of the knee function like a hinge for knee motion. Both the cruciate ligaments and the lateral complex participate dynamically in this increased motion, and the increased number of Ruffini endings could be implicated in this mechanism (Cabuk *et al*, 2016). Golgi-like endings detect the extreme range of joint movement and were most frequent in the cruciate ligaments, particularly the PCL. The primary motion of the knee joint involves flexion and extension. The ACL is a primary means of resistance to hyperflexion, and the PCL provides the primary resistance to hyperextension. Free nerve endings are the predominant mechanoreceptors in the knee capsule and they function as pain receptors in the synovia.

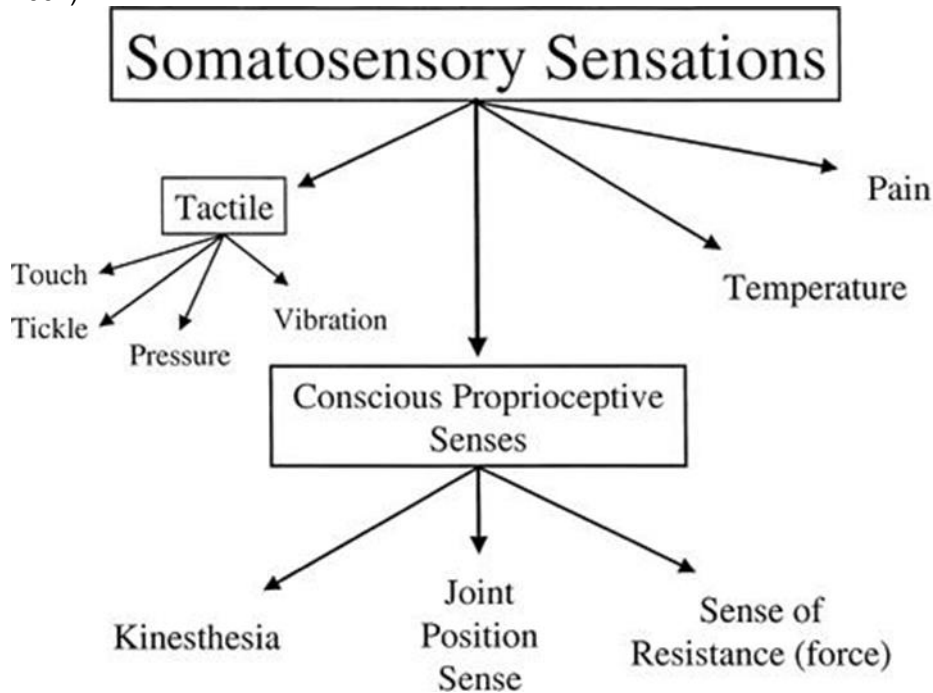
Figure 2.4 Knee articular surfaces and ligaments



(Adapted from <https://boneandspine.com/knee-joint-anatomy/>)

It is evident that the knee joint is richly embedded with afferent innervations consisting of mechanoreceptors that are capable of recording position, velocity, and motion acceleration, pressure and pain. Therefore, this system firstly controls motion with all the relevant regulations needed according to intrinsic and extrinsic factors in every case and secondly maintains joint stability. These functions are fulfilled with spinal and cortical projections of the mechanoreceptors, the spinal reflexes and muscle co-activation. Figure 2.5 illustrates how kinaesthesia, joint position sense and sense of force are regulated from somato-sensory sensations. Therefore, in order to execute functional movements in daily activities, proprioceptive information from a variety of mechanoreceptors is available for central processing.

Figure 2.5 Sensations arising from soma to-sensory sources (adapted from Rienman *et al*, 2002).



Due to deformities in the bodily kinetic chain (i.e. scoliosis) and/or in the knee joint specifically (i.e. varus/valgus deformity) or even due to postural habits, soft-tissue structures (ligaments, muscles, tendons) may have acquired an asymmetrical length-tension relationship. This alteration in length-tension relationship of the soft-tissue of the knee causes an impact on patients' neuro-sensory performance. In osteoarthritic knees there is greater prevalence of varus deformity (92 %) in osteoarthritis of knee and the amount of deformity tends to increase with an increase in the severity of osteoarthritis (Someshwaret *al*, 2018). The prevalence of deformity and angulations is greater in female as compared to male. A comparison of varus versus valgus alignment compared with normal alignment showed that the association of varus alignment with progression was greater than valgus alignment. For every one degree change toward genu valgum, the annual rate of medial cartilage volume loss was reduced by 0.44 %, whereas deformity towards varus alignment reduced the cartilage volume by 0.45 % (Teichtahlet *al*, 2009). Apart from the increased contact stress to the chondral tissue of the knee joint on the medial side of the knee, a varus deformity induces a greater tension to the lateral collateral ligament and a greater slack to the medial collateral ligament. Increase in soft tissue tension will alter the stiffness of the soft tissue complex and may lead to pain on that side (Manning *et al*, 2016). Different strain behaviours have been reported between

the medial and lateral collateral ligaments during knee motion (Jefcotte *et al*, 2016). The impact of changes in soft tissue tension pattern of the knee during motion is not well understood. Increase in tension of the soft tissue complex has shown alteration in voluntary quadriceps muscle activation and changes in muscle strength and gait (Pietrosimone *et al*, 2014). However, inappropriate soft tissue tension may cause increased laxity from the biomechanical point of view, which will lead to poor sensori-motor function and knee instability (Becker *et al*, 2017).

The knee joint is not only comprised of complex articulating anatomical structures but has unequally intricate neuromuscular system, in producing both power and control leading to the generation of force and stability at the joint. The neuromuscular system represents the biomechanical apparatus through which the CNS executes postural actions. The stabilising forces provided by the nervous system's control of muscle activity are of particular interest because this is the only component of dynamic knee stability that can be addressed with therapeutic interventions. Muscle strength, endurance, latency, torque and power, flexibility, range of motion (ROM), and postural alignment all affect the ability of a person to respond to balance perturbations effectively. The ability to produce controlled movement through coordinated muscle activity is commonly referred to as neuromuscular control. Neuromuscular control results from a complex interaction between the nervous system and the musculoskeletal system. There are two primary types of muscle receptors, the Golgi tendon organ and the muscle spindle (please see page 15). The current understanding of these sensory receptors suggests that each organ is connected to a small number of muscle fibres (3 - 25), instead of being attached to many fibres, as was once thought. The number of motor units represented in this small group of muscle fibres is also small (5 - 15) (Rienman *et al*, 2002). Furthermore, evidence suggests that these receptors can respond to forces of less than 0.1 grams. Golgi tendon organs are therefore very sensitive to changes in force and able to provide the nervous system with very specific force feedback. On the other hand, the muscle spindles, are encapsulated structures that range from 4-10 mm in length and lie parallel with muscle fibres. Muscle spindle mechanoreceptors provide the nervous system with information about the muscle's length and velocity of contraction, thus contributing to the individual's ability to discern joint movement and position sense (Shaffer & Harrison, 2007). They consist of specialised afferent nerve endings that are wrapped around modified muscle

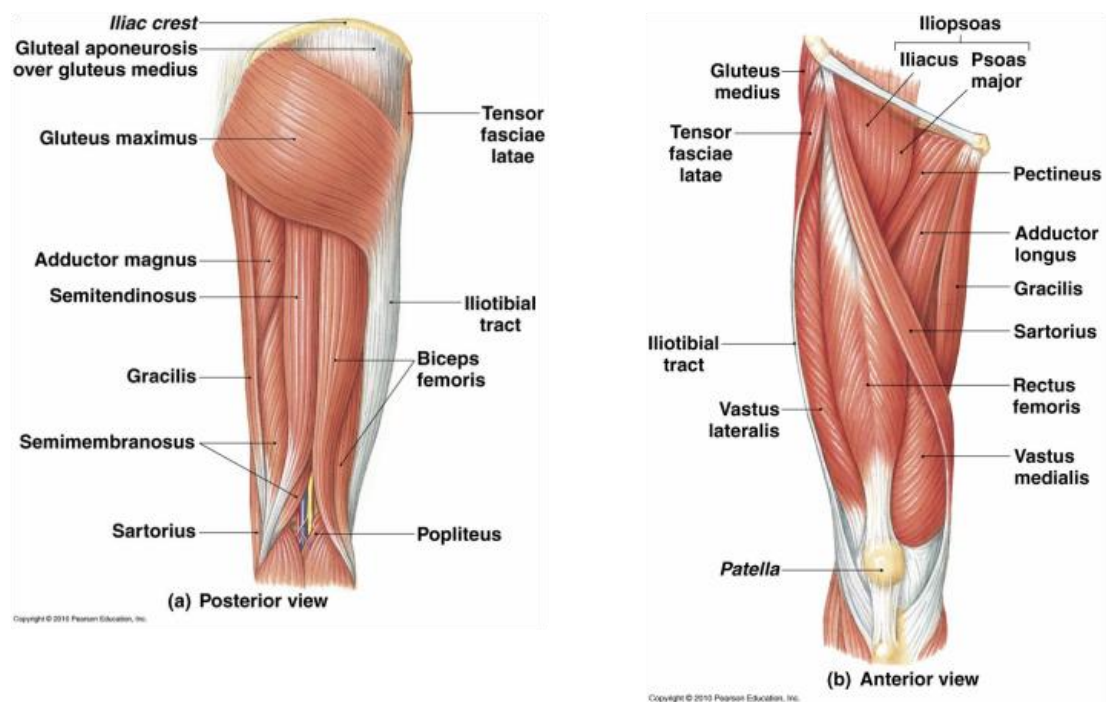
fibres (intrafusal fibres), several of which are enclosed in a connective tissue capsule. There are different types of intrafusal fibres: some are mainly sensitive to changes in muscle length, whereas others are more sensitive to the rate of change in muscle length. Although the central areas of the intrafusal muscle fibres lack contractile elements, the peripheral areas contain contractile elements, which are innervated independent of extrafusal (skeletal) muscle fibres via the gamma motor neurons (γ MNs). Activation of the peripheral contractile elements stretches the central regions containing the sensory receptors from both ends. This results in an increase in the firing rates of the sensory ending and an increase in the sensitivity of the muscle spindle to length changes (Rienman *et al*, 2002). The primary sensory axons (Ia afferents) from the spindle make monosynaptic connections with α -motoneurons in the ventral roots of the spinal cord that, in turn, innervate the muscle within which the spindles are found. This feedback loop is known as the muscle stretch reflex (Williams *et al*, 2001).

The structural unit of a muscular contraction is the muscle cell or muscle fibre, which are supplied by the terminal branches of one nerve fibre or axon. The neural structure whose cell body is located in the anterior horn of the spinal cord, through its relatively large diameter axon and terminal branches, innervates a group of muscle fibres. The term used to describe the single smallest controllable muscular unit, is a Motor Unit (MU). The motor unit consists of a single α -motoneuron, its neuromuscular junction, and the muscle fibres it innervates (as few as 3, as many as 2000) (Basmajian & De Luca 1985). Collectively, all of these influences alter the sensitivity of muscle spindles; thus, the final afferent signals arising from the muscle spindles can be considered a function of both the preceding influential activity and muscle length.

In the knee joint, these receptors can be found in the muscular system relevant for its stability. Specifically, even though the quadriceps muscle has been described as being “the most beautiful muscle” (Last, 1952) other muscles have shown their contribution to the functional stability of the knee. The anterior aspect of the knee consists predominantly of the quadriceps muscles, namely the rectus femoris (biarticular), vastus lateralis (monoarticular), vastus medialis, and vastus intermedius, and the primary function of these muscles is to extend the knee joint. The posterior aspect of the knee consists of the biceps femoris (biarticular),

semimembranosus (monoarticular), and semitendinosus (monoarticular), which form the hamstring group of muscles which function as knee flexors. The secondary stabilisers of the knee joint are all the muscles surrounding the knee alongside the hip muscles and the gastrocnemius muscle. Although their primary function is to produce motion for all the six degrees of freedom of the knee, they also interact with the neuromuscular system to control knee motion, and hence play a vital role in knee SMP (Abulhasan & Grey, 2018). Figure 2.6 illustrates the muscles surrounding the knee joint.

Figure 2.6 The knee joint muscular system.

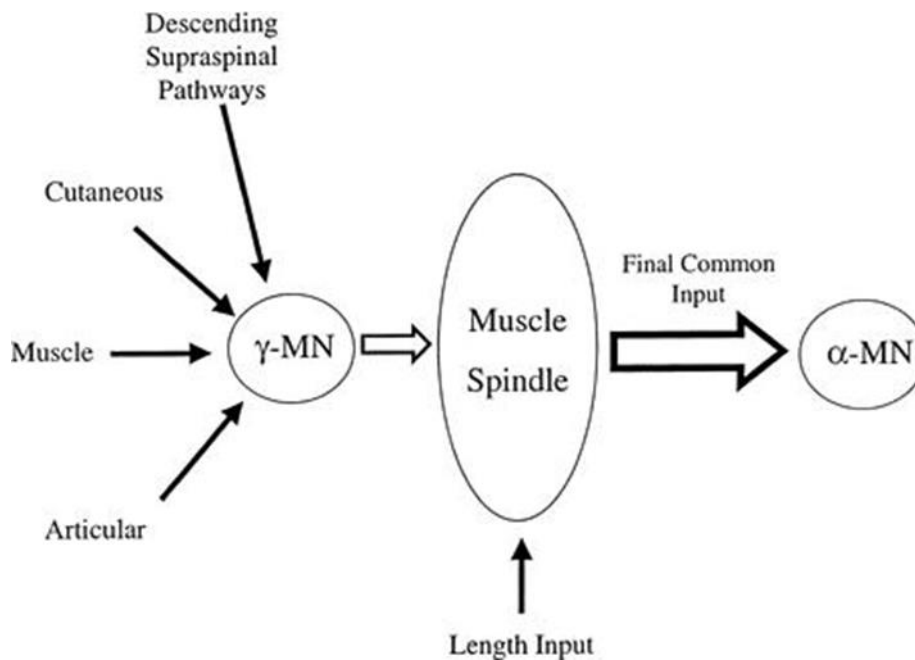


(adapted from <http://cuhsburt.weebly.com/unit-3-skeletal-system-and-unit-4-muscular-system.html>).

2.3 Central processing mechanisms of the sensori-motor system

Figure 2.7 illustrates the hypotheses on how peripheral receptors from cutaneous, muscle (Golgi tendon organs and muscle spindle afferents), and articular tissues, as well as descending commands from supra-spinal areas, converge onto the static and dynamic gamma motor neurons.

Figure 2.7 Convergence hypothesis on influence of ascending and descending commands to gamma motor neurons (adapted from Rienman *et al*, 2002).



The CNS (cerebellum) receives neurologic input from joint position sensors, muscles spindles, and the joint capsule, and this generates neurological feedback from the cerebellum in response to joint movement which aids in maintaining joint stability. The control theory concepts of feedback and feed-forward control mechanisms are typically used to model the function of this system. Dynamic restraints may act, “tense up”, when a stimulus i.e. perturbations expected (feedforward mechanism). In contrast, feedback control should be used to describe actions occurring in response to the sensory detection of direct effects from the arrival of the event or stimulus to the system. Dynamic contributions arise from feedforward and feedback neuromotor control over the skeletal muscles crossing the joint (Finley *et al*, 2009). Underlying the effectiveness of the dynamic restraints are the biomechanical and physical characteristics of the joint (Rienman *et al*, 2002). Although many of the details of the neuromuscular system's control strategy have yet to be precisely defined, the SM system is thought to use a complex control strategy that incorporates both feedback and feed-forward mechanisms. In fact, contribution of feedback mechanisms to postural stability depends on both the level of stability provided by the environment and how the environment influences the pattern of volitional activation (Finley *et al*, 2009). The neurophysiologic evidence suggests that the CNS processes hundreds of thousands of impulses each second,

with input coming from thousands of receptors. This allows the nervous system to obtain a more complete picture of the conditions at the periphery and maintains a level of redundancy within the system at all times. This redundancy of sensory information may allow the nervous system to maintain normal or near normal function despite the presence of errors or a lack of feedback that may occur during unexpected circumstances, such as an injury (Williams *et al*, 2001).

The sensory signals provided by the mechanoreceptors are mediated at three levels in the nervous system: the segmental level of the *spinal cord*, the *brain stem* and *cerebellum*, and the *cerebral cortex*. Each of these regions makes unique contributions to the neuromuscular control system. Most somato-sensory information travels to these higher levels through either the dorsal lateral tracts or the spinocerebellar tracts. The two dorsal lateral tracts are located in the posterior region of the spinal cord and ultimately convey the signals to the somatosensory cortex. Although the majority of the sensations traveling in this tract are touch, pressure, and vibration, various amounts of the conscious appreciation of position and kinesthetic sensations have also been attributed to this tract. The spinocerebellar tracts are characterised by the fastest transmission velocities in the CNS. These supraspinal CNS regions modulate the sensory information from the periphery that enters the ascending tracts (Williams *et al*, 2001). Movement relies on two major nervous system pathways: spinal reflexes and voluntary excitation descending from the motor cortex. The function of these neural pathways dictates the ability of muscles to contract in the periphery.

At the segmental level of the spinal cord, spinal reflexes are produced. Spinal reflexes provide the nervous system with elementary patterns of coordination that can be initiated in response to signals from sensory inputs or descending signals from the brain. The most basic spinal reflexes are monosynaptic reflexes affecting one muscle in which the afferent pathway from the peripheral receptors synapses directly with the a-motoneuron in the ventral horn of the spinal, in the quickest way. For many clinicians, the stretch reflex in response to rapid muscle lengthening provides the most familiar example. However, there are more complex circuits (excitatory or inhibitory) that include additional synapses and result in a coordinated activity of group of muscles (Williams *et al*, 2001). Simulated effusion of the knee

joint causes almost immediate decreases in quadriceps spinal reflexive excitability (Hopkins *et al*, 2001).

The motor responses resulting from sensory input mediated in the brain stem and cerebellum are typically referred to as long-loop reflex. Cerebellum and basal ganglia, are responsible for modulating and regulating the motor commands. They cannot independently initiate motor activity, they are essential for the execution of coordinated motor control at a subconscious level. Learning and anticipation are central features of cerebellar computation and function (Bastian, 2006): the cerebellum learns from experience and is able to anticipate events, thereby complementing active feedback control by an anticipatory feed-forward one (Hofstoetter *et al*, 2002; Herreros *et al*, 2013). The goal of these anticipatory adjustments is to counteract the postural and equilibrium disturbances that voluntary movements introduce. These behaviors can be seen as feedback reactions to events that after learning have been transferred to feed-forward actions anticipating the predicted events.

Despite being the most primitive part of the brain, the brain stem contains major circuits that control postural equilibrium and many of the automatic and stereotyped movements of the body. Areas of the brain stem directly regulate and modulate motor activities based on the integration of sensory information from visual, vestibular, and somatosensory sources (Williams *et al*, 2001).

In general, the motor cortex is responsible for initiating and controlling more complex and discrete voluntary movements. Cortical projections have been reported from joint (both capsular and ligament) afferents, muscle spindles, and Goldgi tendon organs. With respect to conscious appreciation of peripheral receptor stimulation, electric stimulation of both joint and cutaneous (slowly adapting type II) afferent fibres were reported to elicit sensations related to the relevant joint and evoke perceptions of joint movement, respectively. Edin & Johansson (1995) demonstrated that mechanical stimulation of cutaneous receptors elicited kinesthetic sensations. While direct stimulation of a single muscle spindle afferent failed to elicit movement perception, stimulation of several muscle spindles through vibration, and isolated traction, has been reported to evoke conscious movement sensations. The primary motor cortex, receives peripheral afferent information via several pathways and is

responsible for encoding the muscles to be activated, the force the recruited muscles produce, and the direction of the movement. The premotor area, also receives considerable sensory input however, it is mainly involved with the organisation and preparation of motor commands. The supplemental motor area, the third specialised area of the motor cortex, also plays an important role in programming complex sequences of movement that involve groups of muscles. Altered cortical control of the quadriceps has been demonstrated following anterior cruciate ligament injuries (Heroux & Tremblay, 2006) and in those with joint pain (On *et al*, 2004). Cortical excitability may be upregulated following joint injury in surrounding musculature (On *et al*, 2004). While the functional outcome of these alterations remains unknown, it is possible that these increases in cortical excitability may be related to a compensatory neuromuscular strategy used in the presence of a joint injury. Voluntary muscle performance is determined by motor unit recruitment and firing rate, which is potentially influenced by both spinal and cortical pathways.

To summarise, the neuromuscular control system is believed to utilise both feedback and feed-forward control mechanisms. Descending control signals from the brain (e.g. motor programs and responses to visual and vestibular feedback), ensemble feedback from muscle, joint and cutaneous receptors, and the ongoing neural control process for locomotion are involved in a complex interaction through which the neuromuscular system produces coordinated movement. The concept of muscle stiffness modulation is put forth as a key mechanism by which dynamic knee stability may be maintained. Most challenges to knee joint stability alter the force and length feedback of several muscles in the lower limb. As a result, muscle activity patterns are altered in an attempt to maintain stiffness and, indirectly, joint stability. However, our understanding of the neuromuscular control system, remains still somewhat theoretical.

2.4 Somato-sensory, visual and vestibular interactions for balance control

Balance is the ability to maintain the center of gravity of the body within its base of support, with minimal postural sway (Horak, 1987). Balance control depends on the ability to extract peripheral sensory inputs, integrate this information within the CNS, and coordinate and execute an appropriate motor response. Proprioception acuity is an essential component of this sequence of events, providing orientation information about passive and active movements and positions of the joints, as well as the force

resulting from muscular contractions. Healthy individuals predominately rely on their somato-sensory system when they are in a lightened environment with a solid base of support. This somato-sensory system includes both the tactile (sensation of touch and pressure) and proprioceptive system. The CNS processes multimodal afferent input and integrates it at various levels, resulting in efferent processing for coordinated firing of multi alpha motoneurons and their corresponding muscle fibres (Shaffer & Harrison, 2007). The muscle spindles mechanoreceptors (as analysed in the previous section) contribute to the individual's ability to discern joint movement and position sense as well as provide afferent feedback that translates it to appropriate reflexive and voluntary movements (Shaffer & Harrison, 2007). The golgi tendon organ located at the muscle tendon interface relays information about tensile forces, and is sensitive to very slight changes (Shaffer & Harrison, 2007). Balance is achieved by the complex integration and coordination of multiple body systems including the vestibular, visual, auditory, motor, and higher level pre-motor systems (Horak, 1997) (Figure 2.8). Control of balance is complex and involves maintaining posture, facilitating movement, and recovering equilibrium. When postural stability is threatened by destabilising forces, it has been reported that reflex excitability is enhanced independent of changes in volitional muscle activation (Kraus *et al*, 2007). However, in the absence of these forces, it has been proposed that feed-forward, predictive mechanisms may be sufficient to stabilise posture with minimal contribution from feedback mechanisms such as stretch reflexes. reducing the level of support provided by the environment may lead to altered volitional coordination strategies. The combination of both the environment and the volitional strategy will then influence the nervous system's reliance on feedback mechanisms for postural support (Finley *et al*, 2009).

The vestibular and somatosensory systems detect information internal to the body, and the visual system detects information related to the external environment separate from our body. Although it is a known fact that vision is the primary sensory system used in balance (Uchiyama & Demura, 2009); it must be noted that one can stand in the dark and remain upright. While maintaining an upright standing posture while fixating on a point of light fixed in a completely dark room, people may experience a unique sensation that the fixation point is moving but may not perceive their own self-motion. Under these conditions, the person is trying to maintain their postural stability by sensing body sway based on information from various sensory

systems, including (1) the visual system, which detects visual information provided only in the central visual field, (2) the vestibular sensation system, which detects acceleration of the head, and (3) the somatosensory system, which detects plantar pressure (Uchiyama & Demura, 2009). However, research has shown spontaneous lateral body oscillations are largely reduced when standing objects fixate a small light emitting diode in an otherwise darkened environment (Guerraz & Bronstein, 2008). Therefore, postural stability increases with the improvement of the visual environment. The influence of vision depends on task requirements and on age (Kapoula & Thuan, 2006). Because the elderly have a higher dependence on the visual system for postural control than young adults, their fall accidents increase due to impaired visual functions. The sensory system and the development of the individual senses occur in the afferent and efferent motion perception. The afferent motion is the movement of the objects pertaining to the environment; whereas, efferent is consecutive to movements to the eyes, body or head (Kapoula & Thuan, 2006). Results from a study investigating the visual effects on sway responses to support surface tilts suggest that adding the visual cues reduces the contribution of vestibular noise, thereby reducing sway variability and allowing for lower thresholds, which improves the disturbance compensation (Asslander *et al*, 2015). Elderly depend more on the visual information to maintaining postural stability than younger adults. The visual channel is used to convey to the person the direction of a moving object, whereas, the vestibular channel responses exclusively to motion of the head in space and not external phenomena (Guerraz & Day, 2005).

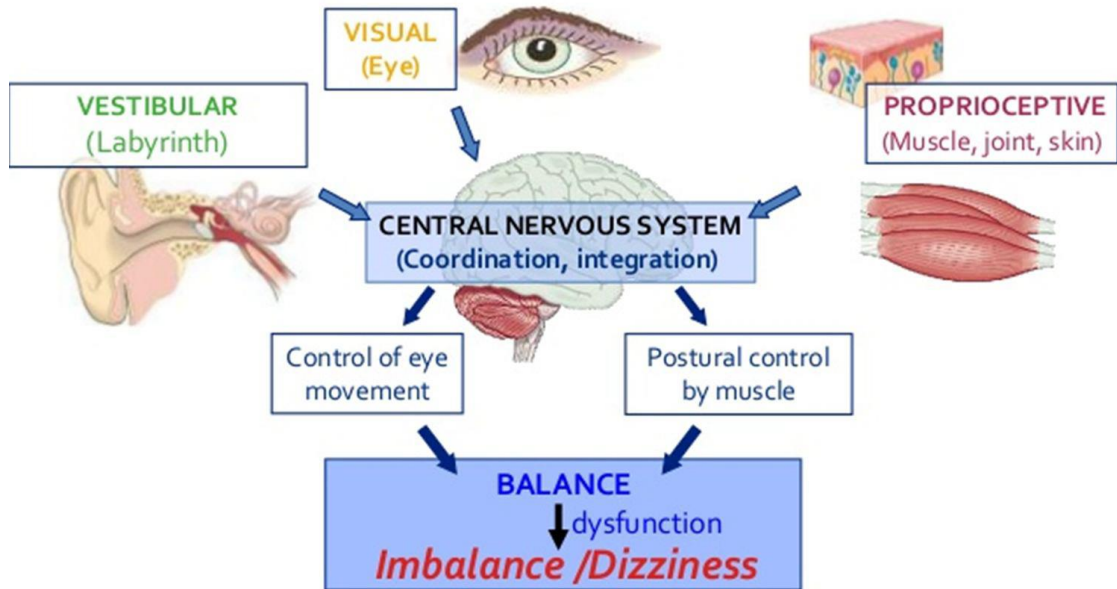
The visual and somatosensory systems interact with the vestibular system throughout the central vestibular pathways and are essential for gaze and postural control. Thus, the vestibular system is unique from other systems because it becomes immediately multisensory and multimodal. For example, the vestibular system interacts with the somatosensory system coupled with corollary discharge of a motor plan allowing the brain to distinguish actively generated from passive head movements (Angelaki & Cullen, 2008). Three roughly orthogonal semicircular canals sense rotational movements, and two otolith organs (the utricle and the saccule) sense linear accelerations. Vestibular afferents are continuously active even at rest and are strikingly sensitive for signaling motion accelerations as our head translates and rotates in space. The vestibular labyrinths provide the detection of head orientation relative to the gravity vector with an accuracy better than 0.5 degrees,

which is about 4 – 5 times better than vision. This accurate detection of head orientation allows postural adaptation relative to gravity preventing imbalance and falls (Kingma *et al*, 2016). Yet, the vestibular system plays an important role in ADL because it contributes to a surprising range of functions, ranging from reflexes to the highest levels of perception and consciousness (Angelaki & Cullen, 2008). The vestibulo-spinal reflexes allow rapid corrections of balance in case of an unexpected balance perturbation. The vestibular senses have a special and non-complementary role. Movement perception and spatial orientation strongly depend on vestibular input and somatosensory substitution and central compensation are insufficient. Interestingly, vestibular stimulation elicits responses only in muscles actively involved in balance control (Luu *et al*, 2012). For example, vestibular-evoked responses are present in leg muscles active in standing balance but responses are absent when comparable levels of activity are generated in the same muscles while standing with the trunk supported (Fitzpatrick *et al*, 1994). In the study by Dakin *et al* (2015) the relative influence of vestibular stimulation on the discharge behavior of motor units in two lower leg muscles that are believed to play distinct functional roles in the maintenance of a stable upright posture was examined. Single motor unit responses to a vestibular stimulus were significantly larger in medial gastrocnemius compared with soleus muscle, indicating that the medial head of the gastrocnemius plays a greater role in vestibular-driven balance corrections during standing balance

It is important to remember that balance control, is required not only to maintain postural stability but also to assure safe mobility-related ADL. However, as aging progresses, the sensory and motor systems involved in the stability of posture and control of the body directions, decline. When balance is impaired in the elderly, the concurrent decline in muscle strength makes it difficult to generate sufficient joint ROM to achieve balance recovery (Carty *et al*, 2012). Jonsson *et al* (2005) have shown an increase in hip muscles activity during quiet stance, an increase in activity of anterior tibialis muscle during the Romberg stance in elderly subjects. Age-related changes in the ability to assess the contribution of proprioceptive inputs relative to those of other sensory inputs become evident under conditions in which the proprioceptive inputs are distorted or distorted and then suddenly restored. Whereas young adults who are healthy, are able to restore balance quickly by taking advantage of sensory redundancy and centrally reweighing available information, older adults do not interpret misleading cues as readily or recognise

and reintegrate accurate proprioceptive information, and therefore can experience postural instability.

Figure 2.8 Somatosensory, vestibular, and visual sensory system interaction (adapted from Samuel *et al*, 2015).



Balance is important in daily activities and is known to be a requirement for maintaining an independent lifestyle in the elderly. In addition, a decline in balance ability is reported to decrease physical function and to increase the likelihood of falling (Jung *et al*, 2015). Constrained balance control potentially underlines dysfunction in sensory deficits or muscle weakness. Clinical balance assessment can differentiate different kinds of balance disorders and a physiological approach can determine underlying sensori-motor mechanisms contributing to balance disorders. Balance and functional joint stability play a crucial role in rehabilitation after injury or surgery for the function of the locomotor system. Therefore, targeted balance rehabilitation training strategies for the elderly through an optimised evaluation of balance characteristics in response to dynamic motions, is considered essential to prevent falls' risk and enhance QoL.

2.5 Physical function, somato-sensory system and effects of physical training

Capability for physical function depends upon many physiological parameters including sensory input from proprioception, muscle strength, visual and vestibular

systems, intact balance systems, range of motion and higher cortical function. Impairments in these parameters are likely to cause disability.

The somato-sensory system and, specifically, the proprioceptive system, are critically involved in the sensory control of balance. A decrease in proprioception acuity (i.e. loss of position, vibration, and tactile sensation) could lead to abnormal joint biomechanics during functional activities such as walking so, over a period of time, which may result in a degenerative joint disease. Colledge *et al* (1994) studied the relative contributions of vision, proprioception, and vestibular system to the balance in different age groups. They found that all age groups were more dependent on proprioception than on vision for the maintenance of balance. However, current evidence has diverted from this notion as a number of studies have confirmed vision as a more important contribution of postural control than proprioception (Hansson *et al*, 2010; Rienmann *et al*, 2003). Additionally, vision is more important to postural control when the proprioceptive information is reduced (Redfern *et al*, 2001), and it is known that older people have to rely more on visual information to maintain balance. Numerous studies have shown optimal control of postural sway is achieved during late adolescence and maintained until about the age of 60 years (Liaw *et al*, 2008). It has been widely reported that proprioception declines during aging process. Thus, impaired proprioception could be a contributing factor to falls.

Regular physical activity may attenuate a decline of sensori-motor function diminished with age. Public health physical activity messages should specifically target older adults whose low activity levels may jeopardize their functional performance. Findings based on over 2,200 persons with radiographic knee OA (Dunlop *et al*, 2010) support clinical advice to patients to engage in physical activity including lifestyle activity and exercise to sustain or improve their functional performance. Randomised controlled trials demonstrate that exercise, muscle strengthening regimes, aquatic therapy and SMT improve performance in walking, stair stepping, and getting in/out of a car (Bartels, 2007; Cochrane, Physical Activity Guidelines Committee, 2008; Ettinger *et al*, 1997; Physical activity guidelines for Americans Department of Health and Human Services, Washington, DC, 2008). Therefore, exercise training is essential for the retention and enhancement of functional and sensori-motor performance.

Gauchard *et al* (1999) investigated the effects of different types of exercise [proprioceptive (group I) or bioenergetic (group II) physical activities and controls only walking on a regular basis], on postural control and balance of aged individuals and concluded that the proprioception can be “trained”, and that regular exercise of proprioceptive nature might be beneficial to retain or regain balance. These findings were corroborated by Tsang & Hui-Chan (2003), who demonstrated that long-term (mean experience ~10 years) Tai Chi (that puts a great emphasis on the exact joint position and direction) practitioners had improved knee joint proprioception.

2.6 Sensori-motor training components

The scientifically-based approach, which can be characterised as a progressive balance training programme using unstable surfaces to provide adequate and safe challenges to the individual’s balance, is SMT. Sensori-motor training addresses both static and dynamic components of balance, as well as the multitude of systems that control balance in order to train effective strategies and elicit automatic postural responses in order to enhance postural stability (Rogers *et al*, 2013). An example of a knee perturbation exercise is presented in Figure 2.9.

Figure 2.9 Perturbation balance exercise (adapted from Fitzgerald *et al*, 2002).



SMT interventions have recently increased in popularity for their utility in rehabilitation, as well as in performance enhancement. While most research on sport-related injuries and performance enhancement is performed on younger individuals, much research is available on age- and inactivity-related changes in the

musculoskeletal system. Therefore, clinicians must combine their knowledge of the human systems that participate in controlling balance with their knowledge of physiologic changes associated with aging in order to determine the most appropriate assessments and interventions for ageing athletes. Table 2.1 presents the basic principles of SMT, as described by Roos (2012).

Table 2.1 Characteristics of sensori-motor training.

- SMT's goal is the improvement of sensori-motor control and functional joint stabilisation.
- The rationale for using SMT, is the existence of sensori-motor deficiencies, symptoms pain, functional instability and functional limitation.
- SMT targets to improve postural control, proprioception, muscle activation, muscle strength and coordination.
- The exercises involve multiple joints and muscle groups, closed kinetic chains in lying, sitting and standing positions.
- Good movement quality with appropriate positioning of the hip, knee and foot relative to each other is essential.
- The level of training is determined by the patient's sensori-motor control and quality of movement.
- Training progresses by introducing more challenging support surfaces, engaging body parts simultaneously, adding external stimuli and varying the type, speed and direction of movement.

These programmes typically take 10 - 20 minutes to perform, 2 - 3 times weekly (Moutzouri *et al*, 2016; Roos, 2012). The effectiveness of this form of training depends on patients 'adherence.

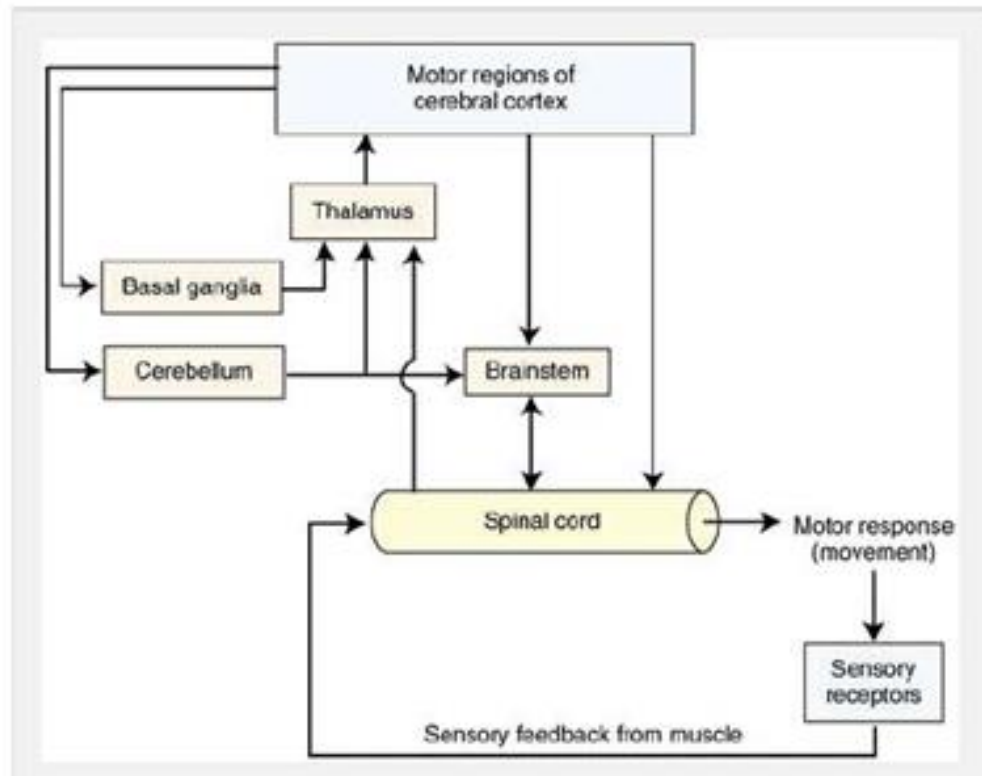
2.7 Mechanism of SMT

The exact mechanism by which SMT improves physical function and joint proprioception precision remains to be clearly understood. SMT-related adaptations could occur at any level of the complex neural pathway involved in the regulation of peripheral sensory integration. Because central and peripheral levels are involved in proprioception, it is not surprising that the explanations for the improvement in proprioception have involved both components during interventions involving physical activity. For example, Zech *et al* (2009) found that

SMT improved dynamic balance in ankle sprain patients and that it resulted in a faster activation of hamstring muscles after a sudden perturbation of stance in patients with ACL rupture. Figure 2.10 illustrates how motor responses are regulated at central and peripheral levels.

Figure 2.10 Kandel hierarchical organisation of the motor system (adapted from Kandel *et al*, 2000. Principles of Neuroscience, 4th Ed. New York: McGraw-Hill).

ORGANIZATION OF MOTOR SYSTEM



At a peripheral level, improvements in proprioception were linked to morphological adaptations in muscle spindle apparatus. Training can induce muscle spindle adaptations at a micro-level, where intrafusal muscle fibres may show some metabolic changes, and at a macro-level, in which the latency of the stretch reflex response decreases and the amplitude increases.

At a central level, physical activity might modify proprioception by modulating the mechanoreceptor gain and inducing plastic changes within the CNS. Previous research however, has shown improvements in dynamic balance tasks and

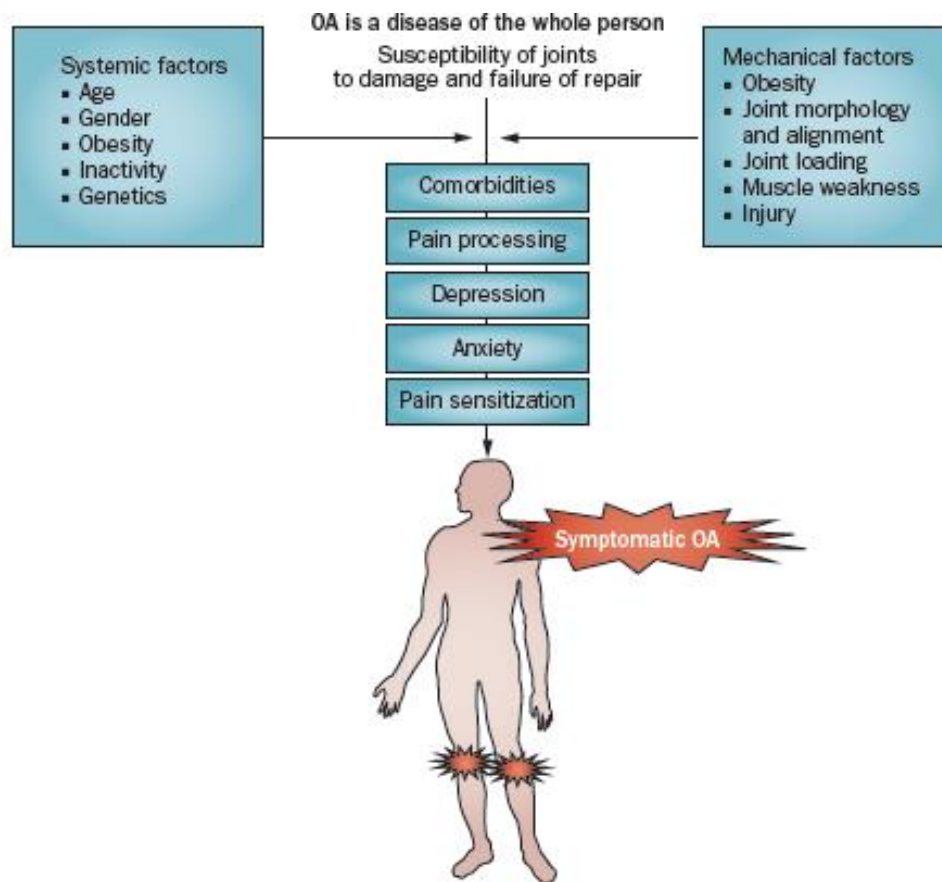
structural re-organisation of grey and white matter after as little as two 45-minute training sessions, when undertaken within a two-week period (Taubert *et al*, 2010).

Sensori-motor training may allow patients to develop adequate motor skills for dealing with potentially destabilising forces on the knee that may be encountered during ADL. It is suggested that the SMT increases coordination between muscle groups and improves the response to sensorial information (Diracoglu *et al*, 2005; Tsauo *et al*, 2008). In SMT, the patient progresses through exercises in different postures, bases of support, and challenges to their centre of gravity. So, each exercise elicits automatic and reflexive muscular stabilisation demanding the patient to maintain postural control under a variety of situations (Kapreli *et al*, 2007; Solomonow & Krosgaard, 2008). Therefore, SMT targets providing external stimuli such as sudden movements, to activate components of sensori-motor system at a local or higher level.

2.8 Osteoarthritis and sensori-motor dysfunction

Optimal functional performance is dependent on the successful management and culmination of critical physiological and psychological processes. These processes involve fatigue, underlying pathology, metabolic changes and possible mental stress because OA is a disease of the whole person (Figure 2.11). Modifiable and non-modifiable systemic and mechanical risk factors contribute to the development of joint vulnerability and eventually to OA. Comorbidities and pain-related factors affect the development of symptomatic OA.

Figure 2.11 A conceptual model of OA (adapted from Roos & Arden, 2015. Strategies for the prevention of knee osteoarthritis, Nature Reviews Rheumatology).



In a normal population, proprioceptive acuity declines with age (related to both central and peripheral changes) (Skinner *et al*, 1984; Ribeiro & Oliviera, 2007) and to a greater extent in the arthritic joint (Roos *et al*, 2011). The neuropathology of proprioceptive deficits (associated with joint injuries or disruption of mechanoreceptors as well as degeneration of their afferent neurons), result in articular de-afferentiation manifestations (impaired joint position sense, balance). Decreased joint space and inflammation alter tension on the capsuloligamentous tissue and may cause proprioceptive deficits (Atfield *et al*, 1996). Both pain and inflammation have the ability to disrupt joint sensibility. Joint laxity, inflammation and pain are closely associated with OA joint pathology (Schmitt *et al*, 2008). Moreover, joint inflammation contributes to arthritic pain, which may impede afferent information and thus impair the precision of joint motion and position sense. Static postural sway in both antero-posterior and medio-lateral direction has been increased in knee OA (Hassan *et al*, 2013). Therefore, these deficits have an impact

on dynamic capabilities of the surrounding muscles and relate to functional stability of the knee.

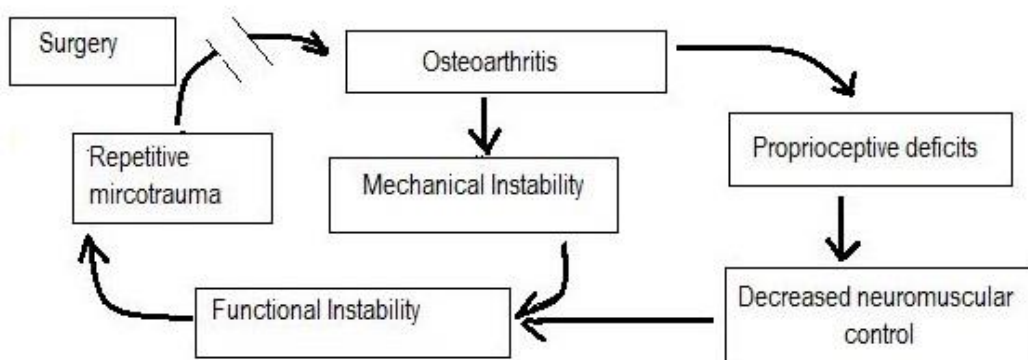
Excessive joint forces damage the articular cartilage, decreasing its capacity to withstand stress and shearing forces between joint surfaces and initiating the chronic cycle of the disease process. Disturbances in the afferent and efferent pathways impair joint proprioception acuity and neuromuscular control compared to age-matched controls (Hassan *et al*, 2001; Koralewitz & Engh, 2000). The chronic presence of degrading enzymes, along with malalignment, changes the length/tension relationship of capsuloligamentous tissues, compromising joint stability. Mechanical strain on nociceptors from local pressure in knee joint effusion during movement, and irritation by inflammatory mediators, result in further decline. The ACL is often lax due to pathological changes. As a result, the knee becomes an inflamed, malaligned and painful joint, with diminished static and dynamic restraints.

A low population of mechanoreceptors in the ligaments associated with degeneration disrupts the mechanical stability, and change OA patients' weight-bearing patterns. Pain also initiates primitive withdrawal reflexes, influencing reflex pathways from the muscle spindle system. Joint effusion further impairs proprioceptive function (Cho *et al*, 2011). Moreover, proprioceptive accuracy has been shown to be impaired in the non-symptomatic knee as well, showing that impairment is not only a local result of the disease (Knoop *et al*, 2011, Sharma *et al*, 1997). Knee instability is a complaint of some people with knee OA and leads to a lack of dynamic control during mobility (Fitzgerald *et al*, 2004; Schmitt *et al*, 2008).

Proprioceptive deficits could also predispose individuals to OA by altering motor control (Roos *et al*, 2011). For example, in an OA knee joint, sensori-motor dysfunction may cause greater impact of the limb during heel-strike, and therefore initiating or perpetuating joint damage. Abnormal afferent information in the OA joint is believed to be responsible for arthrogenous muscle inhibition, which is characterised as the inability to produce full voluntary muscle activation (MVA) (Hurley *et al*, 1997). Electromyographic studies have shown that the painful knee joint is associated with an increase in quadriceps' activity that is thought to result from abnormal discharge of muscle, tendon and joint receptors (Hiranaka & Takeuchi, 1995). Muscle weakness, impaired mechanoreceptors and altered

walking patterns cause degenerative changes in patients suffering from knee OA (Knoop *et al*, 2011). Figure 2.12 depicts the detrimental viscous circle of OA on mechanical instability and neuromuscular control.

Figure 2.12 Influence of OA on mechanical instability and functional stability (reproduced from Lephart SM, Henry TJ. The physiological basis for open and closed kinetic chain rehabilitation for the upper extremity. *J sport Rehabil* 5:71-87, 1996).



An association between quadriceps sensori-motor dysfunction and disability has been established, emphasising the importance of quadriceps exercise in the management of knee OA (Hurley & Scott, 1998). It has been suggested that good sensori-motor function is of importance for reducing knee injury (Hewett *et al*, 2007), and for achieving better objective and patient-reported measures (PROMs) after injury (Herrington, 2006). Elucidating the aetiology of proprioceptive deficits in knee OA is essential because proprioceptive acuity may be modifiable, and restoration would promote stability, falls' prevention and better functional performance (Lephart *et al*, 1997). Therefore, the need for a relevant review of the literature on the recovery of sensori-motor deficits after surgery (Chapter 5), and the efficacy of SMT is highlighted (Chapter 6), as mentioned in the aims of the thesis (Introduction).

It was observed that a substantial number of OA patients reported the sensation of knee instability (buckling, shifting, or giving way of the knee) during ADL (Fitzgerald *et al*, 2004). A regression analysis indicated that patient' reports of the knee giving way, buckling, or slippage and affecting physical function, goes beyond the point where the phenomenon can be explained simply by contributions from impairments such as knee pain, range of motion, and quadriceps strength. This finding may imply that knee instability is a problem that should be specifically addressed in rehabilitation programmes, and may require interventions beyond

those that address pain, joint motion, and muscular strength, to maximise the effectiveness of rehabilitation for individuals with knee OA.

Exercise is a component of the management guidelines for knee OA among numerous professional rheumatologic and health societies, as it appears to reduce pain and improve function. Results from recent studies in knee OA suggest exercise, predominantly isolated dynamic strengthening exercise, provides small-to-moderate benefits for pain and function (Iversen *et al*, 2010). In addition, trials of exercise appear to be well tolerated by patients and present little risk. Appropriate treatment modalities for individuals with knee OA include, exercise (land-based and water-based), strength training, education, and weight management according the OARSI non-surgical guidelines (McAlindon *et al*, 2014). It is plausible expectation that the addition of SMT to the rehabilitation programme of these patients could produce more positive effects on balance and functional activity levels (Ahmed *et al*, 2011), underpinning the primary aim of the main study (addressed in Chapter 8).

Evidence-based evaluation and treatment guidelines recommend the use of non-operative treatments before surgical treatment options are considered. When non-operative treatment fails, surgical options such as TKR are available. Knee replacement is indicated for end-stage degenerative knee joint disease, as evidenced by radiographs, and persistent pain, disability and limited function after all conservative treatment measures have been exhausted (Manen *et al*, 2012).

2.9 TKR surgery

Total knee replacement has been reported as a very successful end-stage surgical procedure for relieving chronic knee pain with relatively low risks, despite differences in patients' status and the type of prosthesis used (Anderson *et al*, 1996; Ewald *et al*, 1999). The main indication for TKR is OA, which accounts for the clinical rationale/justification of more than 94% of TKR operations, along with post-traumatic arthritis and rheumatoid arthritis (Hospital Episode statistics online; Juni *et al*, 2003; Manen, 2012). Patients present with excellent implant longevity, with modern prosthetic designs reaching a survival rate of 15 years or more for 90 % of surgeries (Gill & Joshi, 2001). Total knee replacement can typically improve debilitating joint pain (Konig *et al*, 2000) and functional limitations (Heck *et al*, 1998; Walsh *et al* 1998). The goals of TKR include reducing pain, returning to ADL,

preserving the joint line, balancing the ligaments, and restoring mechanical alignment.

Total knee replacement involves a surgical procedure replacing the damaged or diseased knee joint surfaces with an artificial joint. The surgery involves exposure of the front of the knee, with detachment of part of the quadriceps muscle (vastus medialis) from the patella. The patella is displaced to one side of the joint, allowing exposure of the distal end of the femur and the proximal end of the tibia. The ends of these bones are then accurately cut to shape using cutting guides oriented to the long axis of the bones (Health Quality Ontario, 2005). The cartilage and the ACL are removed; the PCL may also be removed, but the tibial and fibular collateral ligaments are preserved. Metal components are then impacted onto the bone or fixed using polymethylmethacrylate cement. Alternative techniques exist that affix the implant without cement. The latter cement-less techniques may involve osseointegration, including porous metal prostheses. The replaced joint, shaped to allow motion of the knee, relies on the surrounding muscles and ligaments for support and function. Figure 2.13 illustrates OA of the knee and arthroplasty treatment.

Figure 2.13 (a) Radiograph of OA knee, (b) intra-surgery image with damaged areas of articular bone exposed and (c) post-operative radiograph of TKR treatment (adapted from knee replacement seminar Carr *et al*, 2012).



Although TKR is a well-established treatment, it is constantly evolving with ongoing advancements in surgical technique, medical technology and prosthesis design. Most TKR designs have kinematics which differ from the normal knee, while unicompartmental knee arthroplasties have shown nearly normal knee kinematics. Cruciate retention and patellofemoral intact compartments in bi-unicompartmental knees are more likely to provide normal control of knee motion (Zanasi, 2011). There is no

consensus as to whether to use a PCL-retaining design or a posterior-stabilized (PS) design for TKR (Jacobs *et al*, 2011) although the presence of mechanoreceptors is shown in histologic analysis to be maintained in PCL-retaining TKR (Mihalko *et al*, 2011). The presence or retention of mechanoreceptors and innervations of the ligament may indicate an advantage when retained during TKR and is beneficial in stability and function. Previous arguments for selecting cruciate-retaining or posterior stabilised knee prostheses have focused on biomechanical issues, but the neurosensory contribution of the posterior cruciate ligament has also been considered to be an important factor in the selection of the implant design. Proponents of cruciate-retaining designs have theorised that preserving the PCL for its neurosensory properties is advantageous to patients and contributes to a more normal gait and “feel” of the knee after TKR; however, research substantiating these proprioceptive benefits with either prosthetic design has been contradictory. During one year follow-up, patients with PS-TKR reported greater functional limitations in squatting, kneeling, and gardening compared to PCL-retaining designs. On top of this the PS models seem to be unable to imitate the functional capacity of PCL particularly in high-demand activities that involve deep flexion, and thus leading to motion limitation (Conditt *et al*, 2004). The results from the study by Simmons *et al*, (1996) and Swanik *et al*, (2004) did not identify any proprioceptive or kinesthetic advantages of preserving the PCL. Sensory denervation of the posterior cruciate ligament begins early in the OA knee. Consequently, the prospect that mechanoreceptors repopulate the posterior cruciate ligament and are responsible for enhanced joint sensation is limited. More recent evidence concerning the prosthetic design have shown that PCL-retaining implants contribute to a greater improvement in sensori-motor performance (JPS, TTDPM), than PS models (Skarpas *et al*, 2017).

More recently, partial knee replacement-more commonly known as bi- or unicompartmental knee replacement (UKR) has seen resurgence in interest and popularity. Although generally considered a more difficult procedure than TKR, UKR is thought to allow preservation of the uninvolved soft tissue and bone, reduced operating time, better post-operative range of motion, less pain, better stair-climbing ability, improved gait due to proprioceptive maintenance and increased patient satisfaction than TKR (Dalury *et al*, 2009). Unicompartmental knee replacement can provide advantages over TKR however, appropriate patient selection and careful

surgical technique is required. Combined with the use of minimally invasive surgery (MIS) techniques, gender-specific prosthetics and computer-assisted navigation systems, orthopaedic surgeons are now able to offer patients knee replacement procedures that are associated with (1) minimal risks during and after surgery by avoiding fat embolism, reducing blood loss and minimising soft tissue disruption; (2) smaller incisions; (3) faster and less painful rehabilitation; (4) reduced hospital stay and faster return to normal activities of daily living; (5) an improved range of motion; (6) less requirement for analgesics; and (7) a durable, well-aligned, highly functional knee. However, there is no evidence of superior functional benefit of MIS techniques than those managed with the traditional approach.

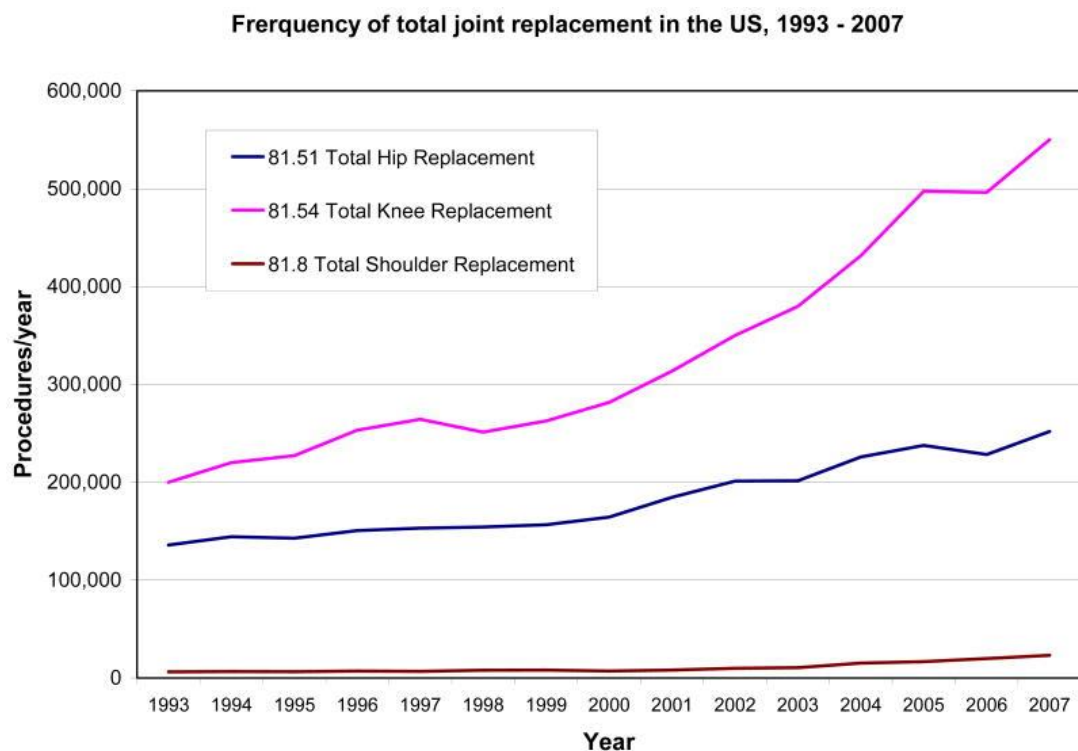
Different surgical approaches and advances in biomaterials and tissue engineering will continue to create exciting new opportunities in the management of OA. However, other surgical approaches than TKR have specific indications in terms of age groups, joint surface environment, course of arthritic progression etc. and cannot be applied to the wide population of OA patients (Katz *et al*, 2010). The evidence supporting the use of many surgical approaches is limited by weak study designs and small samples. Advances in the field will need to couple scientific insights with rigorous studies of the efficacy and cost effectiveness of surgical approaches to OA management. According to researchers from the Medical University of Graz (Austria) reported at the EFORT Congress in Istanbul (2013) analysing data from eleven relevant national or regional registers about the procedure and replacement rates of knee prostheses as well as the age of the patients, Dr Sadoghi, author of the study reported: "The rate varies between 40 and 163 procedures per 100,000 inhabitants, the average being 106." Amongst the countries being compared, total knee replacement is undertaken most frequently in England, Denmark, Norway and Sweden in relative terms and least frequently in New Zealand, Australia and Canada. In the study by Kremers *et al*, (2015) a little over 2 % of individuals in the United States were living with a total hip or total knee replacement in 2010. This corresponds to an estimated seven million people, including 620,000 individuals who underwent both procedures. These numbers underscore the large number of Americans who have benefitted from these procedures. Given the success of total hip and knee replacement in improving function and quality of life of individuals with severe arthritis, the current trends will likely continue in the coming decades. Therefore, TKR was selected as the surgical

approach more frequently reflecting surgeon's choice for the management of the OA population.

2.10 TKR epidemiology

In 2008, 650,000 TKR procedures were performed in the United States (Kin *et al*, 2011). More than 77,500 primary TKRs were performed in the United Kingdom in 2009 (National Joint Registry, 2010). The rates for TKR in the United States have risen from 31.2/100,000 person-years in the 1970s to more than 220/100,000 person-years in 2008 (Singh *et al*, 2010). By 2007, over 550,000 TKR were performed in the US (Katz *et al*, 2011; Figure 2.14). Women are more likely to undergo TKRs than men with a ratio of 1.4/1, which was the same ratio 15 years ago (Culliford *et al*, 2010). A significant increase in the future incidence of TKR is also expected, since statistical projections between 2005 and 2030 in the USA, have shown that the demand for TKR will grow by 673 % compared to an 173 % increase in THR (Kurtz *et al*, 2007). The mean age of patients undergoing TKR in UK is 70 years and the rate for TKR is greater in women than in men with a ratio of 1:4 (Culliford *et al*, 2010).

Figure 2.14 Annual frequency of total knee, hip and shoulder replacement in the US, 1993–2007.



2.11 Total knee replacement surgery designs and neuro-sensory properties

Total knee replacement successfully addresses some of the deficits and functional limitations associated with knee OA deconditioning. During TKR, articular tissue that house joint mechanoreceptors and intra-articular structures of the knee joint, including the ACL, cartilage and menisci, are permanently resected. Subsequently, the replaced knee has been deprived of a major proportion and variety of key proprioceptors, deteriorating the pre-surgery joint environment. Moreover, oscillations used by the knee joint to regulate postural control are unlikely to reach a detectable threshold by sensory receptors in the replaced knee (Cash *et al*, 1986). Presumably, additional proprioceptors from all of the capsular and musculotendinous receptors need to compensate feedback for the loss, in order to maintain stability and balance, albeit at reduced levels of capability (Andriachi *et al*, 1986; 1993; Warren *et al*, 1993). Different types of prostheses and retention of the PCL also have an impact on joint translation and mobility components, which are important for proprioceptive ability (Attfield *et al*, 1996; Barrett *et al*, 1991; Skinner *et al*, 1984). Skinner *et al* (1984) suggested that the loss of proprioception due to arthritis was not improved by surgery. By contrast, Barrett *et al* (1991) claimed that when joint alignment and the 'joint space height' is reconstituted, the sense of position is improved, indicating that the reloading of lax collateral tissues at the time of the operation may be beneficial. Moreover, it has been shown that soft-tissue balance (length-tension relationships for PCL and collateral ligaments) after surgery in both flexion and extension is important for allowing satisfactory post-operative proprioception of the knee (Barret *et al*, 1991). Any difference in the tension of the medial and lateral collateral structures may therefore be perceived as a varus or valgus movement of the leg and may produce an antagonistic and corrective action from the hamstrings and quadriceps muscle groups, thus affecting proprioception (Barrett *et al*, 1991). Tension of the soft tissue envelope of the knee shows direct impact on knee function after TKR. Inappropriate soft tissue tension may cause increased laxity from the biomechanical point of view, which will lead to knee instability and poor function. Knee instability after TKR is the cause of revision surgery in up to 25 % and knee stiffness in 10–15 % (Dalury *et al*, 2013; Singh *et al*, 2016). It has been shown that pain predominantly occurs at the medial and lateral retinaculum and might be the cause for increase in pain, when the implantation of a total joint causes tightness of the soft tissue structures (Dye *et al*, 1998).

The stiffness of the soft tissue complex in OA knees was studied in extension and flexion. The stiffness in extension and flexion was 8.9 and 8.5 N/mm, respectively, with a soft tissue tension of 60 N and increased to 26.6 and 21.4 N/mm with a tension of 180 N (Asano *et al*, 2008). The authors of the aforementioned study concluded that soft tissue tension during surgery of 80–160 N appears to be appropriate from the clinical point of view as it does not affect post-operative range of motion. The accurate soft tissue balance was also investigated in human cadavers and showed an inverse relationship of laxity and contact force (Manning *et al*, 2016). Preservation of the correct soft tissue tension during TKR is very demanding. Manual stress testing, spacer blocks, tensiometers and navigation are all used in TKR to preserve static and dynamic soft tissue constraints. Even when TKR surgery is performed very precisely, differences in kinematics and soft tissue restraints occur. The usage of a tensiometer is helpful to adjust the distraction force when creating the extension and flexion gap during replacement surgery. Taking into account all the aforementioned literature, a number of factors could intrude as a result of surgery that could actually have an impact on patients' neuro-sensory performance.

Different prosthetic designs appear to offer some biomechanical advantages. There are three different types of knee replacement prostheses. Non-constrained prostheses use the patient's ligaments and muscles to provide the stability for the prosthesis. Semi-constrained prostheses provide some stability for the knee and do not rely entirely on the patient's ligaments and muscles to provide the stability. Constrained prostheses are for patients whose ligaments and muscles are not able to provide stability for the knee prosthesis.

In a recent study (Baghdadi & Abdaallah, 2014), three different types of TKR designs were compared regarding pain, balance and functional performance effects 1) PCL-retained 2) posterior stabilised and 3) unicompartmental (UKR). They found that the UKR design, probably due to preservation of all structures in one compartment of the knee, is more advantageous in pain reduction, function and balance of patients. Amongst the PCL-retained and the posterior stabilised prosthesis, the PCL-retained was preferable, with better performance outcomes for patients.

Maintenance of proprioception input from the PCL has been suggested as a potential benefit of PCL retensioning during TKR (Andriachi *et al*, 1982). Increased physiologic knee motion and extension mechanism function appear to result from the use of prostheses designed to retain the PCL. Moreover, retaining the PCL, offers advantageous neuro-sensory properties in the joint and contributes to a more normal gait pattern and stair-climbing (Andriachi *et al*, 1982). However, the literature still provides conflicting evidence regarding PCL-retained prostheses, with the argument that the PCL in a degenerated joint, has lost its tension and sensitivity, and therefore cannot promote better motion sense accuracy compared to a PCL-substituted prosthesis (Simmons *et al*, 1998). A systematic review conducted by Sierra & Berry (2008), concluded that although PCL-retained is a more demanding surgical procedure, it is associated with better long-term outcomes, with the provision that PCL can be properly tensioned intra-operatively.

Therefore, as the TKR procedure is currently performed, consideration to preserve as much soft-tissue components of the knee as technically possible, or restoration of sensori-motor mechanisms of the knee intra-operatively, remains crucial for patients' recovery of sensori-motor function.

2.12 TKR outcome

Knee replacement has resulted in substantial gains in QoL for people with end-stage OA. From a patient's perspective, in a five-year follow-up of patients undergoing TKR, compared to their pre-surgery condition, marked improvement was noted in pain (95 %), deformity corrections (90 %), walking ability (80 %), and stair climbing (55 %) (Konig *et al*, 2000). After TKR, 75 %-89 % of patients report being satisfied (Vissers *et al*, 2010). Interestingly, functional capacity and actual daily activity do not contribute to patient satisfaction. Patients with a better self-reported mental functioning pre-operatively, as well as patients with less pain experience, presented with fulfilled expectations post-operatively (Vissers *et al*, 2010). Therefore, psychological distress seems to be an issue affecting QoL after TKR surgery (Westby & Backman, 2010; Mizner *et al*, 2010; Nilsson *et al*, 2009; Salmon *et al*, 2001). Interestingly, TKR patients experience a significantly poorer functional outcome than THR patients five to eight years post-operatively (Jones *et al*, 2007).

A number of clinical and research investigations have reported marked outcome variations following TKR compared to pre-surgery. Patients' performance-based activity limitations worsened early after surgery (compared to the pre-surgery condition). At 12 months, all of the patient-reported and performance-based measures of activity improved compared to tests at one month (Mizner *et al*, 2011). The PROMs of activity limitations did not reflect the acute worsening of performance-based based activity and physical impairments. Acute changes in patient-reported outcome after TKR suggest that patients dramatically overestimate their functional ability early after surgery. Moreover, although PROMs show marked improvement, probably due to pain elimination, residual deficits in ROM, muscle recruitment and SMP, have been observed up to seven years following TKR. Therefore, a significantly poor impact on functional status (i.e. postural stability, walking speed, stair ascent/descent) is evident even in the long-term (Benedetti *et al*, 2003; Brander *et al*, 2006; Gauchard *et al*, 2010; Ishii *et al*, 1997; Mizner *et al*, 2005a,b, 2010; Mizner & Snyder-Macker, 2005; Ouellet, 2002; Pap, 2000; Valtonen *et al*, 2009; Van der Linden *et al*, 2007; Walsh, 1998; Yakhdani *et al*, 2010; Yoshida *et al*, 2008). This discrepancy suggests that patients' concerns and priorities differ from those of surgeons and clinicians.

Overall, the effectiveness of TKR has been supported by twenty-one studies that had reported pre-operative and post-operative outcome scores for patients undergoing TKR, and which had offered the mean effect score and the percent change in performance. The 21 studies included patients of various ages, which had used a variety of prostheses and techniques to implant the device. The revision rates ranged from 0 % to 13 % in the studies reporting at least five years of follow-up (Health Quality Ontario, 2005). Interestingly however, there is some research to suggest that TKR surgery accelerates OA in the contra-lateral limb, probably due to altered biomechanics of the operated limb (McMahon & Block, 2003).

The pioneering days of TKR have probably ended, and future emphasis should first be on patient selection for surgery and improvement on patients' rehabilitation programmes.

2.13 Factors affecting recovery after total knee replacement

The literature has provided evidence for a number of factors such as obesity, sex (female), older age, and previous surgical interventions to be implicated as pre-operative predictive factors of poor outcome (pain and function) and increased complication rate (deep vein thrombosis, infection, stiffness, loosening, and osteolysis [the softening and loss of bone]) (Lizaur *et al*, 1997; Singh *et al*, 2008; Vincent *et al*, 2008). Comorbidities such as the presence of low back pain and mental health seem to affect post-operative improvement (Escobar *et al*, 2007). Furthermore, retaining the PCL during TKR has demonstrated beneficial effects in ADL, closest restoration to function and greatest patient' satisfaction (Conditt *et al*, 2004).

It is of considerable interest to determine how TKR affects patients' physical performance and influences the disability resulting from OA. Following TKR, a number of non-resolved symptoms often affect a sufferer's mobility and independence in posing a burden on their QoL (Cushnaghan *et al*, 2009; Mizner *et al*, 2010; Nilsson *et al*, 2009; Rastogi *et al*, 2008; Salmon *et al*, 2001). Although gradually improving, muscle weakness, stiffness, balance and sensori-motor deficits continue to persist up to ten months in these patients (Gauchard *et al*, 2010; Ishii *et al*, 2010; Mizner *et al*, 2005; Yoshida *et al*, 2008; Valtonen *et al*, 2009). Finally, psychological distress associated with functional limitations may further compromise recovery (Andersson *et al*, 1996; Westby & Backman, 2010). Therefore, apart from demographic factors or factors related to the type and selection of TKR surgery that cannot be modified with physiotherapy, muscle weakness, joint stiffness, and sensori-motor performance deficits need to be mitigated with targeted exercise training. The latter processes underpin the main (Chapter 8) and secondary aims of the thesis (related to perceived 'gaps' in the relevant literature) (Chapter 5 and 6).

The extent of functional limitations post-TKR have been studied, although often not holistically, since isolated measurements of pain and knee ROM cannot effectively evaluate surgery outcome, and both patient and health professional views are needed (Mizner *et al*, 2010; Westby & Backman, 2010). The implications of OA pathophysiology and TKR surgery will be discussed further (in the next section, 2.14) across all parameters of performance and disability. The section will consider

drawbacks and benefits of the procedures, on which post-operative physiotherapy should focus, in order to optimise recovery.

Despite being thought of as determining the outcome of recovery to a certain extent, only isolated investigations of indices of sensori-motor, neuromuscular and psychophysiological performance have been reported. Particular interest would focus on the understanding of alterations to the relationships between indices of: i) objectively-measured function and PROMs, and ii) patterning of changes amongst indices of functional, balance-related, sensori-motor, neuromuscular and musculoskeletal performance, after the effect of SMT has been determined. The latter would permit the identification of potential drivers of the mechanisms for change in functional performance. Therefore, the conclusions that might arise from an in-depth investigation of these potential relationships may have a significant impact on identifying a more holistic approach to assessment and to selecting the best possible training interventions in patients following TKR.

2.14 Implications of TKR

2.14.1 Functional performance

There is good evidence that in the short-term, TKR is a safe and cost-effective intervention in patients that do not respond to non-surgical therapies such as medication and physiotherapy (National Institutes of Health, 2004). Studies have demonstrated good outcomes of TKR even in elderly patients, in which complications and risk of mortality is involved (Hamel *et al*, 2008). In a prospective study of patients with severe OA, the group in which TKR surgery had been performed demonstrated substantial improvement in functional scores and ADL compared to a non-surgical group at a one year follow-up(Hamel *et al*, 2008). Furthermore, in a survey of patients who underwent TKR, patients reported improvement in their ability to walk and climb stairs (Hawker *et al*, 1998). Although functional recovery post-TKR reaches the pre-operative level, which is already impaired due to pain and disuse, rarely does it achieve the level of aged-matched controls (Walsh, 1998; Yoshida *et al*, 2008).

There are a few studies investigating recovery to ADL of patients undergoing TKR. More specifically, in a study of elderly patients (>75.2 years), recovery in their abilities began with assessment of the ability to get up and out of a chair without

assistance and an ability to go to the bathroom, within a period of in an average of seven days, with the ability to walk within twelve days and dress within fourteen days (Hamel *et al*, 2008). Mizner *et al* (2005) reported that patients' performance in climbing stairs and "stand up and go" returned to pre-operative levels two months after surgery. Moreover, recovery in independent bathing came within twenty-one days, food preparation within twenty-one days and housework within forty-nine days, whereas the ability to go shopping became feasible within 60 days. Outdoor activities such as gardening were performed after six months (Hamel *et al*, 2008).

Change in physical impairment at one month post-surgery showed muscle weakness (50% loss), loss of motion (25 %) from the pre-operative state. The assessment of physical function beyond the acute recovery is a key component, as patients' outcomes normally do not stabilise until six months post-surgery. Improvement in knee function during walking and ADL tasks is indicated even seven years post-surgery, even with an overall decreased physical performance ability (Van der Linden *et al*, 2007). Improvement in this case is more likely attributed to increased muscle strength and balance or re-training of pre-surgery habitual patterns. Mobility recovery has been strongly associated with quadriceps muscle power and BMI (Lamb & Frost, 2003). Consequently, the understanding of recovery and surgery implications (Chapter 5) on functional performance, balance and falls' risk is important in order to enhance physiotherapeutic assessment and and to provide an improved focus on aspects of training.

Studies investigating long-term effects are limited to the study by Cushnaghan *et al* (2009). In this study, patients and matched controls were followed-up using questionnaires, from the time they were on the waiting list for TKR, until approximately six years post-surgery. Bearing in mind the limitations inherent in an observational study design, results showed a sustained beneficial impact in aspects of physical function of the Short Form 36 Health Survey (SF-36) following TKR without however, noting concomitant differences in aspects of mental health. The latter is noteworthy in a population context of concurrent ageing and functional decline.

Gait analysis provides both quantitative and qualitative data to assess performance, strength, and functional status following TKR. The relationship between progressive recovery of muscle strength and its influence on gait patterns has not been fully elucidated. A number of studies have been performed using gait analysis post-TKR, to investigate and observe asymmetries, kinematic (knee joint motion and loading patterns) and kinetic (muscle force patterns) parameters (Benedetti *et al*, 2003; Wilson *et al*, 1996). Post-operative status of patients' gait has been found to be improved in terms of speed, cadence and stride length compared to pre-operative performance, but still lags well behind age-matched healthy individuals (Yoshida *et al*, 2008).

In terms of gait characteristics, patients tended to walk with decreased knee flexion excursions and less peak knee flexion at three months, accompanied by an increased hip moment, and with the stance phase of the operated side diminishing at the same time (McClelland *et al*, 2007; 2009; Yoshida *et al*, 2008). Research within this field of study has shown less knee flexion during swing and greater knee flexion during stance phase even two years post-operatively (Benedetti *et al*, 2003; Fuchs *et al*, 2002). Kinetic findings indicate that in the sagittal plane, patients following TKR tend to walk in a different manner than controls, and this has been attributed to reduced proprioception. However, it is not unrealistic to consider the effect as being residual from the pre-operative condition (McClelland *et al*, 2007). At twelve months, speed and time of stance were normalised between limbs; whereas, knee flexion excursions remained at the previous observed levels. Decreased knee flexion after heel-strike can influence shock absorption and the demand on the quadriceps. On the coronal plane, knee abduction moment has been found to be increased while adduction moment was decreased (Benedetti *et al*, 2003; Hatfield *et al*, 2011). While this decreased adduction moment potentially reduces loading in the medial compartment of the knee, at the same time, it has been closely associated with the unwanted implications of prosthesis loosening (Hilding *et al*, 1995). Most parameters seem to be improved from the pre-operative condition. This is with the exception of a decreased external rotation moment in the early-stance compared to the pre-operative condition, which does not go along with normal gait pattern (Hatfield *et al*, 2011). Altered kinematics after TKR can be explained on the grounds of changed biomechanics under weight-bearing conditions, impaired proprioception, or continuation of pre-operative habits. Consequently, muscle recruitment

measurements, accompanied by muscle architecture parameters, could provide a clearer picture about the mechanisms by which muscle weaknesses might be implicated in the capability to undertake functional tasks (within the aims of Chapter 8).

In terms of muscle activation during gait, prolonged activity of rectus femoris, hamstrings and tibialis anterior during stance phase have been found as persistent abnormal kinetic characteristics even two years after TKR (Benedetti *et al*, 2003). The reduced knee flexion excursion during loading is often followed by a reduced internal extension moment, therefore placing fewer loads on the knee extensors. More specifically, Andriachi *et al* (2003) identified a gait pattern that tended to extend the knee throughout the stance phase, and thus avoiding demands on the quadriceps. This is known as a 'quadriceps avoidance gait' that has previously been seen in patients following ACL injury. As a result, although scoring on functional tasks reached that of healthy controls at twelve months, patients needed to compensate for their muscle weakness by utilising the unaffected side (Yoshida *et al*, 2008). From a clinical perspective, it can be assumed that there is a threshold above which quadriceps' strength can influence knee kinematics during gait, but not necessarily facilitating the maintenance of full function. Consequently, physiotherapy practice should aim at re-gaining quadriceps muscle strength in patients that would be above the assumed threshold to diminish asymmetries. Conditioning should provide adequate stimuli to reduce reliance on compensatory mechanisms, and promote proprioceptive acuity and symmetry. One of the innovative aims of the main study (Chapter 8) will be to challenge the relevant knee muscles through SMT to adapt and offer full bilateral potential following TKR surgery.

Moreover, patients undergoing TKR, due to the sedentary life imposed by debilitating pain, present with marked cardiovascular deconditioning (Naylor *et al*, 2010), affecting their execution of ADL and capacity to exercise. In a study by Yakhdani *et al* (2010), treadmill walking speed was examined in OA patients before and after TKR. Mean maximum walking speed pre-operatively was $0.9\text{m}\cdot\text{s}^{-1}$, $0.8\text{m}\cdot\text{s}^{-1}$, six weeks post-TKR, $1.1\text{m}\cdot\text{s}^{-1}$ six months post-TKR and $1.1\text{m}\cdot\text{s}^{-1}$, one year post-TKR. However, the results are in accordance with the study by Walsh *et al* (1998), in which although walking speed improved one year after TKR, it did not reach levels of healthy age-matched controls. As a result, the increase in walking

speed between pre-surgery and post-TKR is a clinically significant improvement, and may be related to the patients' higher confidence in joint stability. Joint excursions however, were not investigated in this study. Van der Linden *et al* (2007) had found patients with slightly slower walking speed pre-operatively ($0.79 \text{ m}\cdot\text{s}^{-1}$), which reached $1.20 \text{ m}\cdot\text{s}^{-1}$, 18-24 months post-surgery and $0.95 \text{ m}\cdot\text{s}^{-1}$, seven years post-surgery. The decline seven years later may be attributed to a number of factors, including age and end of physiotherapy sessions. Therefore, unless targeted specific rehabilitation training is offered, functional performance is impaired for the first 2 – 3 months post-TKR, then gradually improved, compared to pre-surgery levels, but does not reach the level of aged-matched individuals.

2.14.2 Balance-related performance and sensori-motor performance

As previously discussed, knee OA patients present with SMP deficits (Hurley *et al*, 1997; Pap *et al*, 2000; Sharma *et al*, 1997) and a pathological gait pattern (Messier *et al*, 1992; Viton *et al*, 2000). However, the influence of TKR on proprioception acuity remains unclear. Some studies have documented benefits from the procedure on postural control and proprioception (Harato *et al*, 2009; Swanik *et al*, 2004), whilst others have not observed any substantial improvement (Fuchs *et al*, 2002; Konig *et al*, 2000; Pap *et al*, 2000). Degeneration of joint elements, pain, stiffness and decreased level of activity prevalent in OA, alter muscular and joint afferent input and thus, affect stability (Fitzgerald *et al*, 2004; Tijon *et al*, 2000). Besides, the dependence on the vestibular and visual systems for balance, proprioceptive information deriving from tendons, muscles and capsule decreases with age, causing instability and risk of falls.

During TKR, intra-articular structures of the knee joint, including the ACL, cartilage, and menisci are resected. Subsequently, the replaced knee has been deprived of fundamentally important proprioceptors, deteriorating the pre-surgery joint environment. Moreover, postural oscillations used by the knee joint to regulate control are unlikely to reach a detectable threshold by sensory receptors in the replaced knee. Different types of prostheses and retention of the PCL also have an impact in joint translation and mobility components, which are important to proprioceptive ability. Decreased muscle strength, ROM, and altered movement patterns evident post-surgery, affect sensory and mechanical function of the joint. On the other hand, reduced pain and inflammation observed post-surgery potentially

improves kinesthesia (Swanik *et al*, 2004). Yakhdani *et al* (2010) showed that the rate of falls was decreased post-operatively, with twenty-one falls in the preceding year before surgery and up to seven falls, one year post-TKR. In a study by Gauchard *et al* (2010), comparison of patients post-TKR (TKR1), with patients following a six-week rehabilitation protocol (TKR2) and controls, in static and dynamic postural examination, showed that TKR1 patients lacked postural stability. However, post rehabilitation, TKR2 patients exhibited skills close to the quality of balance stability of controls.

The intra-sensory environment of the knee has been significantly changed by altered movement patterns, proprioceptive and strength deficits associated with OA disease, alongside with structural and biomechanical changes of the replaced knee. Interestingly, although the effect of TKR on proprioception remains controversial, balance appears to be enhanced. Visual and vestibular systems feed information for postural control. Presumably, balance control is enhanced by the contributions of additional proprioceptors outside the joint capsule and an increase in the sensitivity of proprioception derived from the muscles surrounding the knee joint, which in turn, act together to compensate for the loss of somato-sensory input due to surgery. Moreover, generation of compensatory movements may be possible due to regulation from the ankle and the hip sensori-motor strategy (Gauchard *et al*, 2010). The re-alignment of knee joint post-surgery (correction of varus/valgus deformity) provides more effective sensory regulation. Finally, the progressive recovery of motor function (occurring though at a later stage and being optimal between 6 - 12 months post-surgery) is also advantageous post-TKR. However, rehabilitation can be a key component triggering the aforementioned strategies and enhancing both proprioceptive and balance' control.

2.14.3 Neuromuscular performance

It has been found that OA patients present with profound reductions in muscle activation especially in the quadriceps, which is considered one of the mechanisms involved in muscle weakness and atrophy. This lack of full voluntary-activation (VA) is termed VA deficit or arthrogenous muscle inhibition (Rice *et al*, 2010). One possible explanation is that knee joint receptors contributing to the regulation of muscle tone and movement by influencing the gamma muscle loop to enhance stability and stiffness, are inhibited by acute inflammation (Cervero *et al*, 1991;

Neugebauer *et al*, 1994). Quadriceps' weakness is widely reported in patients with TKR and has a substantial impact on movement patterns, gait, and functional impairments (Mizner *et al*, 2005a, b; Mizner & Snyder-Macker, 2005). Reduced quadriceps' strength pre-operatively does not recover fully, causing a substantial impact on patients' movement patterns, gait, and function (Berman *et al*, 1991; Mizner *et al*, 2005a, b; Mizner & Snyder-Macker, 2005). Quadriceps' strength recovery is essential within the early post-operative period (up to two months post-surgery), since it enhances functional loading and dynamic joint stability (Cademartiri & Soncini, 2004). Declines of 21 % to 42 % in muscle strength (compared to non-operated limb) following TKR have been reported at six months (Berman *et al*, 1991). These declines are found to persist to a smaller extent, 12 % to 29%, even at two years (Berman *et al*, 1991). This loss in muscle strength is also evident in the cross-sectional area of the muscle (CSA), as measured by computed tomography (CT scan), reaching a 14 % loss at ten months post-surgery, a finding that was clinically associated with functional limitations (Valtonen *et al*, 2009). Therefore, measurement of muscle strength associated with measurements of muscle architecture in patients post-TKR, can inform clinicians on the potential mechanism underlying muscle weakness exhibited in functional tasks and which might be further addressed in rehabilitation (within the aims of main study, Chapter 8).

There has been an attempt to predict functional status and outcome up to two years post-TKR by investigating relationships in parameters such as age, BMI (body mass index), sex, strength, ROM and self-perceived functional scores (Jones *et al*, 2003; Mizner *et al*, 2005; Zeni & Snyder-Mackler, 2010). From the above mentioned factors, greater quadriceps' muscle strength and pre-operative knee flexion ROM predicted improved outcomes. Consequently, functional impairments post-TKR appeared to depend upon patients' pre-operative clinical condition. Furthermore, strength deficits of the non-operated side seem to be also implicated in poorer outcomes (Zeni & Snyder-Mackler, 2010). A number of studies have investigated post-operative recovery of the quadriceps' and the hamstrings' muscle groups following TKR. At one month after surgery, quadriceps' strength has decreased by up to 60 % of the pre-surgery level, despite early usual care therapy (Mizner *et al*, 2005; Stevens *et al*, 2010). Mizner & Snyder-Macker (2005) showed that at three months post-TKR, strength asymmetry between limbs in the quadriceps' muscle

was related to knee flexion excursion differences during the stance phase. A study by Yoshida *et al* (2008) investigated strength, physical function, ROM and motion analysis during gait between three and twelvemonths post-surgery, comparing a sample of twelve patients following TKR with matched controls. All clinical measures showed significant improvements for the involved knee. In fact, quadriceps muscle strength reached 66 % of the non-operated side within the three month period and almost equivalent levels (88 %) at twelve months, although it still remained weaker than controls.

Fewer studies have concurrently investigated hamstrings' muscle strength, but it is believed to recover faster than that of the quadriceps' (Berman, 1991). One month post-TKR, hamstrings' strength had decreased by up to 50 %. At six months after surgery, although hamstrings muscle group strength' has reached pre-surgery levels, the quadriceps muscle had remained up to 25 % weaker than pre-surgery. When compared to healthy age-matched controls, quadriceps' and hamstrings' strength of the operated leg was weaker by up to 40 % (Stevens *et al*, 2010). An important finding was that hamstrings' co-activation increased at one month post-TKR during maximal quadriceps' tasks, implying decreased stability and risk of overuse tendinopathy, and therefore post-operative pain (Stevens *et al*, 2010).

In relation to changes that are more chronic, Berth *et al* (2002) investigated the long-term effects (three years) of TKR on quadriceps' VA in both operated and non-operated knees by evaluating the peak force during maximum voluntary contraction (MVC) in a specially-designed dynamometer. They used the twitch interpolation technique as an established method for evaluation of muscle function in the knee joint (Hales & Gandevia, 1988; Hurley *et al*, 1997), and which involves additional external muscle stimulation when MVC has not reached its complete potential. The VA of the operated knee improved after surgery but remained lower than that of matched controls. The deficiency of full activation of the quadriceps muscle actually affected both sides to a similar extent, although it also seemed to depend on the type of surgery, the follow-up assessment and essentially the physiotherapy rehabilitation programme (Machner *et al*, 2002). Moreover, in terms of physiotherapy practice, focus on the hamstrings muscle group should happen as has been previously noted, as muscle co-activation has been shown to be elevated one month post-operatively. Therefore, early targeted conditioning interventions of knee muscle

groups post-surgery, potentially involving not just isolated muscle strengthening, may be a key component in the attempt to reverse the deficits of neuromuscular performance presented.

2.14.4 Musculoskeletal performance

There is no consensus on how stiffness after TKR is defined. However, it is widely thought of as being represented by $>10^\circ$ of extension lag and/or $< 95^\circ$ of flexion at six weeks (Kim *et al*, 2007). The literature has reported 6.3 % of operated knees with fixed flexion problems (Lam *et al*, 2003). Improvement of knee stiffness has been indicated post-TKR, but only modestly in patients presenting with poor pre-operative ROM (McAulley *et al*, 2002; Myles *et al*, 2002). Guidelines for the best results post-TKR suggest that patients should achieve $<5^\circ$ of extension and $>125^\circ$ of flexion (Rehabilitation guidelines by The Specialty Team for Arthroplasty Rehabilitation [STAR] Team in conjunction with the UW Health Joint Replacement Surgeons, 2014). Lam *et al* (2003) showed a specific pattern encountered in terms of ROM at six weeks and at one year post-TKR. Knees with lower initial flexion, gain movement within this time period, whereas those with greater flexion tend to lose ROM at six weeks, but improve again in the later stages. During functional tasks, OA knees exhibit 28 % reduction in joint excursion, compared to healthy matched controls (Lam *et al*, 2003). Four months post-TKR, this reduction is further worsened by up to 55 %; only 2 % of patients improved in knee motion in the period of 18 - 24 months post-operatively compared to the pre-operative values (Myles *et al*, 2002). Nevertheless, even at seven years after surgery, patients were still showing accumulating gains in knee flexion, beyond that seen at twenty months post-TKR, showing that recovery of functional knee motion extends more than two years after surgery (Van der Linden *et al*, 2006). Although these observations appear to indicate a slight improvement from the pre-operative state, healthy matched controls are still superior in ROM.

Reduction of knee flexion makes stair-climbing and functional tasks such as walking over an obstacle, more difficult. More specifically, Byrne *et al* (2003) reported that patients following TKR, present with increased hip flexion to compensate for the decreased knee flexion during walking over an obstacle, either due to joint stiffness or to the weakness of knee flexors. As a result, deficits in knee ROM lead to

alterations in the strategy used to perform functional tasks, which may affect the stability and balance control capabilities of these patients.

More recent studies have focused on the potential benefit of newly designed prostheses to facilitate greater degrees of flexion. In this sense, it has been reported that patients with higher degrees of flexion ($>125^{\circ}$ - 140°) demonstrate optimal stair-climbing (Meneghini *et al*, 2007). Nevertheless patient satisfaction and perceived QoL has not been correlated with the increased amount of flexion ($>95^{\circ}$) obtained post-surgery (Miner *et al*, 2003).

Knee extension has been found to improve even three years post-surgery (Aderinto *et al*, 2005). At hospital discharge, amongst other physiotherapy goals is the attainment of full extension (with a window of 5° – 10° lag) and 90° of knee flexion. The latter capabilities are considered necessary for carrying out ADL, such as getting up from a chair, ambulation, and climbing stairs. In cases of flexion contracture, overall knee function is affected and ADL activities become more tiring physiologically. Extension lag leads to greater muscular energy consumption from the quadriceps group. Patients following TKR have reported a decreased level of satisfaction compared to age-matched controls when performing certain activities such as kneeling or squatting that require higher degrees of flexion (Devers *et al*, 2011). However, there is no comparison reported for the pre-operative state in this respect.

Quadriceps' antagonist reflex, controlling pain, may cause difficulty in the restoration of joint excursion after TKR (Cademartiri & Soncini, 2004; Spencer *et al*, 1984). The literature relating to the implications of TKR on ROM is limited. However, compromised knee joint ROM, already observed from the pre-operative period, is found to be a predictive factor of the improvement shown post-TKR (Bade *et al*, 2014). Pre-operative flexion has been considered a robust determinant of post-operative flexion (Ritter *et al*, 2007). Pre-operative stiffness is considered mild for flexion $>70^{\circ}$, moderate between 50° - 70° , and severe $<50^{\circ}$ (Massin *et al*, 2010). However, there was no difference in capacity indicated between good and poor flexion ($<90^{\circ}$) in the kinematics of well-aligned prostheses (Pereira *et al*, 2008).

Multiple factors can have an impact on the ROM after TKR. The latter include peri-operative complications, PCL tightness, surgical technique, malposition of femoral or tibial components, the presence of posterior osteophytes, patient motivation, and the physiotherapy protocol (Laskin *et al*, 2004). In a study of 5,622 conventional TKRs, Ritter *et al* (2007) found the incidence of postoperative fixed flexion contracture to be 3.6 %. Interestingly, not BMI but male sex, increasing age, and the presence of a pre-implant fixed flexion contracture were identified as risk factors for developing fixed flexion contracture post-operatively (Goudie *et al*, 2011; Ritter *et al*, 2007). No speculation as to why the latter factors affected flexion contracture has been offered in the literature.

Pre- and post-operative flexion contractures, as well as post-operative hyperextension, have been found to be associated with poorer post-operative outcome and pain (Ritter *et al*, 2007). Post-operative pain is a common experience during the acute and post-acute phase and can therefore interfere with the normal recovery. Most frequently, pain is implicated with complications such as infection, prosthesis loosening, reflex sympathetic dystrophy, and less often with normal recovery parameters such as scarring. In a study of 439 TKRs performed by one surgeon, 46.2 % of patients reported no pain, 46.7 % occasional pain and 7.1% almost no pain (Ritter *et al*, 1997). Although TKR contributes to the overall well-being of the patient, the literature suggests that it also leads to a reduced range of active and functional motion in the majority of patients. This is associated with a lower-than-normal physical QoL. Therefore, measurements of ROM alongside with measurements of performance can help obtain a better understanding of the limits and determinants of patients' functional ability and perceived scoring.

2.14.5 PROMs of pain, function and psycho-physiological performance

Pain is a primary factor in limiting the muscle force and load exerted in the replaced joint. Restoration of minimal levels of arthrogenic pain and normal nociceptive responses is the primary objective for both patients and orthopedic surgeons. From a patients' perspective, pain improved in 95 % of TKR surgeries in a five year follow-up study (Konig *et al*, 2000). Unless post-operative complications are present, pain is expected to be diminished significantly post TKR (Douglas, 2004; Ritter, 1997). Relevant literature has shown that pain relief is the most rewarding benefit post-TKR surgery, especially after acute surgical implications have subsided. Therefore, pain

will be used in the current study as a candidate outcome of perceived recovery and functional status, as well as an important indicator of capacity to comply with the prescribed exercise load. Scrutiny of an index of pain within the relevant review of clinimetric quality of outcomes will potentially endorse both its use in this thesis and its clinical utility (within aims of Chapter 3).

Traditionally clinicians rely on PROMs to monitor patient's perspective of clinical outcome. Self-reported questionnaires typically reflect patients' perception on a range of functional tasks as well as their perception of emotional health (Alviar *et al*, 2011; Dowsey & Choong, 2013). Patient-reported outcomes after TKR generally reflect an improved functional performance, balance confidence and satisfaction on health-related quality of life, 2 - 3 months after surgery (Hawker *et al*, 1998; Gandhi *et al*, 2009; Heiberg *et al*, 2010; Mizner *et al*, 2011; Stevens *et al*, 2011; Swinkels *et al*, 2009; Yoshida *et al*, 2008). Self-reported outcomes have been closely related to pain relief after TKR (Mizner *et al*, 2011). For that reason, PROMs (SF-36, Knee Outcome Survey – Activities of Daily Living Scale [KOS-ADL]) have been frequently found to present improvement of greater magnitude (ES= 1.7 - 2.2) compared to that estimated by physical performance measures (ES=0.6 - 0.8) (Mizner *et al*, 2011; Stevens *et al*, 2011; Yoshida *et al*, 2008).

Contemporary (usual care) physiotherapy regimes post-TKR, which will be discussed next, reflect the initial design of rehabilitation strategies to manage post-surgery patient' deficits.

2.15 Evidence on usual care rehabilitation post-TKR

Physiotherapy rehabilitation has traditionally focused on exercises addressing pain, strength, ROM, and gait re-education (Codine *et al*, 2004; Dauty *et al*, 2007; Lowe *et al*, 2011; Moffet *et al*, 2004; Worland *et al*, 1998). Several studies have recently included exercises with an emphasis on function (Frost & Lamb, 2002; Moffet *et al*, 2004) that have consistently showed significant benefit in mobility and functional status at least on mid-term follow-up.

Besides medical interventions to alleviate pain, in most cases patients are prescribed physiotherapy according to health care system' policy. Strengthening exercises, ROM exercises, continuous passive movement (CPM), patella

mobilisation, massage, electrical muscle stimulation, and gait re-education are interventions frequently used for the management of patients following TKR (Codine *et al*, 2004; Dauty *et al*, 2007; Frost *et al*, 2002; Lowe *et al*, 2007; Moffet *et al*, 2004; Worland *et al*, 1998). Moreover, outpatient physiotherapy versus cost-effective supervised home regimes have been investigated (Barrois *et al*, 2007; Cook *et al*, 2008; Coulter *et al*, 2009; Genet *et al*, 2007; Kramer *et al*, 2003; Mockford *et al*, 2004; Moffet *et al*, 2004; Rajan *et al*, 2004). Clinical guidelines suggested for these patients (Genet *et al*, 2007), have to date, not fully determined the required components of exercise therapy or the milestones needed to be achieved for the advancement of exercise therapy during the rehabilitation process.

An emphasis on functional programmes for the past 15 years has also been one of the cornerstones to achieve patient independence (Frost *et al*, 2002; Genet *et al*, 2007; Moffet *et al*, 2004) and has been suggested as a successful and standardised way forward for patients after TKR. After hospital discharge and according to each country's health systems' directives and patients' needs, physiotherapy is continued at a rehabilitation center, at home with supervision or on an outpatient basis. Ouellet *et al* (2002) emphasises the necessity of post-discharge physiotherapy due to the quadriceps' loss of strength at two months post-surgery. A study by Rajan *et al* (2004) suggested that most patients would do sufficiently well with inpatient physiotherapy followed by clear instructions and a home exercise regime, and therefore, there is no need for outpatient physiotherapy. While, although the benefit of a cost-effective strategy of a home exercise regime is highlighted, findings should be viewed with considerable skepticism since the only outcome measure used had been ROM. Although results depend upon physiotherapy practice, patients' satisfaction seems greater when receiving outpatient physiotherapy (Mahomed *et al*, 2000; Moffet *et al*, 2004). However, no statistically significant differences have been reported in outcome measures between home-based and outpatient-based modes of practice (Mahomed *et al*, 2000). A number of studies have investigated the rehabilitation outcome of patients managed through home care physical therapy following TKR. So far, findings encourage direct discharge to home-based rehabilitation as a rationale use of resources and a viable option for many patients (Froimson, 2013; Chimenti & Ingersoll, 2007; Roos, 2003). Consequently, home management should be considered as an option for clinical practice as it seems an effective mode of rehabilitation and would be considered to be less expensive.

Home management has been provided to patients when it's supervised directly by a community physiotherapist, or indirectly via a booklet or telephone supervision (Frost *et al*, 2002; Kramer *et al*, 2003). Kramer *et al* (2003) performed a RCT involving 160 patients and comparing results of a four-month clinic-based rehabilitation (two-hourly sessions per week) with those from a home-based daily self-managed exercise programme, supervised by telephone using outcomes of pain and functional performance. Although a number of patients were lost at follow-up, with the majority of those being in the home-based group, the two groups had performed equally well at one year. Kolisek *et al*, (2000) investigated a simple self-rehabilitation programme, continued at home post-discharge, without physiotherapy supervision, and which had shown improvements in functional ROM for most patients with no post-operative secondary problems having been encountered by patients. Therefore, within the main study aims' (Chapter 8), is one to implement a supervised home-based programme, as it represents a strategy for cost-effective management of clinical care. This approach would be considered to have a further advantage of patients being in their own environment and thus, avoiding the necessary time and effort to travel to the hospital with potential adverse consequences for patients' adherence to the prescribed levels of training.

Another potentially important factor that has received little scrutiny in the literature is that of the recommended volume of exercise training that would enhance recovery performance in a functional-based programme. Moffet *et al* (2004) investigated the potential benefit of an intensive functional rehabilitation programme versus standard care and found significant improvements in pain, ambulation capacity (9%) and functional status as measured by a relevant questionnaire. Table 2.2 presents an analytic description of published rehabilitative protocols of intensive functional exercise programmes re-produced by Meier *et al* (2008). These protocols recommend three days of inpatient rehabilitation after TKR, followed by 2 - 3 weeks of home physical therapy visits. Finally, approximately four weeks post-TKR, a six-week programme of outpatient rehabilitative exercise is recommended, specifically designed to address patients' functional impairments and muscle strength deficits. Two studies have introduced the use of neuromuscular electrical stimulation (NMES) to speed up the recovery of quadriceps in parallel with the aforementioned exercise programmes (Avramidis *et al*, 2003; Mizner *et al*, 2005). The NMES offers an innovative approach to potentially mitigate quadriceps muscle VA deficits and

prevent muscle atrophy early after surgery. While this approach might restore normal quadriceps muscle function more effectively than voluntary exercise alone, it would not be logistically available to patients' post-TKR, especially in a home-based care.

Table 2.2 Description of standardised functional exercise therapy programmes (adapted from Meier *et al*, 2008, p. 251).

	Moffet <i>et al</i> , 2004	Avramidis <i>et al</i> , 2003	Mizner & Stevens, 2005
Modalities			
Start of programme	8 weeks post-TKR	1 day post-TKR	3.5 weeks post-TKR
Frequency	1-2/week	Twice daily	3/week
No of visits	12(8 weeks)	16 (8 days)	18 (6 weeks)
NMES		x	x
warm-up and stretching			
1. Active ROM	x	x	x
2. Ankle pumps	x		
3. Hamstrings stretching	x		
4. Mobility of neck, upper limbs, and back	x		
specific strengthening			
1. Quadriceps sets	x	x	x
2. Hamstrings sets	x	x	
3. Hip abductors	x		x
4. Lunges			x
5. Straight leg raise	x	x	x
functional task-oriented			
1. Sit-to-stand	x		
2. Standing terminal extension	x		x
3. Wallsquats/ standing squats	x		x
4. Standing hamstring Curl	x		x
5. Stairs	x		x
6. Walking backward, and/or laterally	x		
7. Walking in place with large amplitude of hip and knee flexion and upper-limb movements	x		
Endurance			
1. walking	x		
2. Stationary cycling	x 5-20 min	x 5-10 min	x 10-15 min
Cool down			
1. Slow walking	X		
2. Stretching	X		
3. Ice	X		

NMES: neuromuscular electrical stimulation; ROM: range of motion; TKR: total knee replacement; min: minutes.

The physiotherapy rehabilitative protocol post-TKR focuses on the achievement of functional ROM, increased muscle strength and ambulation, with the least possible dependence. Attainment of improvement is signified by reduction of pain and functional recovery according to the safety limitations that each rehabilitation phase poses. Standard care refers to the continuation of hospital exercise programmes that had been previously taught to patients during their hospital stay, at home. Usual exercise regimes incorporate isometric muscle contraction exercises, dynamic quadriceps' exercise between 0° - 30° of knee flexion, straight leg raises, active flexion exercises, and often CPM (Beaupre *et al*, 2001). Therefore, the content of functional rehabilitation programmes offered in the literature share similarities in terms of context, with significant emphases on regaining effective ROM and functional performance in patients who've undergone TKR. The aims of this thesis include determining through a clinical survey, the current usual care practice programmes offered in Greece and to compare it with that offered by the literature (Chapter 4).

Rehabilitation following TKR plays a major role in determining the optimal clinical outcomes and patient satisfaction. Recent rehabilitation trends that are discussed next (section 2.16), support early and aggressive regimes to be implemented in patients post-TKR (Cook *et al*, 2008; Isaac *et al*, 2005; Lowe *et al*, 2007; Moffet *et al*, 2004; Rossi *et al*, 2010; Zeni & Snyder-Mackler, 2010).

2.16 “Gaps” in literature regarding TKR rehabilitation care

Patients' expectations of outcome following TKR are not always met, with as many as 20 % reporting no improvement or continuing to endure knee pain and have problems after TKR (Beswick 2009; Nilsson 2009; Vissers 2011). As such, additional ways to improve treatment outcomes are warranted. Alongside these findings, QoL in patients following TKR can be affected significantly by residual limitations in functional performance. Therefore, post-operative care and rehabilitation is one of the priorities for the sufferers in order to overcome pain and ameliorate the limitations observed for patients undertaking ADL. Accumulating evidence supports the use of accelerated rehabilitation during a hospital stay (five to seven days) without detrimental effect on patients' mobility or function (Cook *et al*, 2008; Isaac *et al*, 2005; Klika *et al*, 2009; Oldmeadow *et al*, 2002; Thomas *et al*, 2003). Treatment for patients after hospital discharge should involve either

outpatient physiotherapy sessions or supervised home-based programmes, according to the health-care resources of each country, patients' needs, clinical pathways and physiotherapy strategies (Barrois *et al*, 2007; Cook *et al*, 2008; Coulter *et al*, 2009; Genet *et al*, 2007; Kramer *et al* 2003; Mockford *et al* 2008; Moffet *et al*, 2004; Rajan *et al*, 2004).

At the same time, there is no consensus on the most appropriate characteristics for an exercise programme, in terms of dose (volume/intensity) that should be prescribed during post-surgery rehabilitation. Moffet *et al* (2004) first implemented an intensive programme of functional training, with specific parameters in terms of intensity and duration of exercise, but without observing any adverse joint-related effects. Rossi *et al* (2010), within a case-report study, investigated performance and function by implementing a medically-based training programme involving a progressive increase of exercise volume. Having derived a one-repetition maximum (1RM) in an initial strength test by patients, this was used to modulate a gradual increase in exercise intensity each week, and any pain or swelling were recorded as criteria for patients to be working within safe limits. However, the optimum intensity and concomitant volume that should be recommended for the safest and most effective treatment, has yet to be clarified. Relevant research investigating sensori-motor training, has added these components on to the standardised functional training, without commenting on the volume or progression of the rehabilitation programme. Therefore, included within the main study' aims (Chapter 8), is the evaluation of the early clinical effectiveness of usual care practice (functional exercise training) integrated with novel sensori-motor elements, delivered in a time-matched prescribed programme.

2.17 Evidence on current novel interventions within rehabilitation regimes post-TKR

Current novel rehabilitation trends involve a) more intensive muscle strengthening (Bade *et al*, 2011; Rossi *et al*, 2010) b) combination of NMES with resistance training (Avramidis *et al*, 2003; Stevens *et al*, 2012), c) addition of sensori-motor components (Gstoettner *et al*, 2011; Piva *et al*, 2010), and d) in-home tele-rehabilitation sessions post-TKR (Toussignat *et al*, 2011). In a recent case-report, an early (two weeks) and more aggressive (in terms of progressively increased resistance) closed-chain exercise programme added within a medical exercise

therapy regime, showed early strength recovery and a fairly equal weight distribution over limbs in functional tasks such as sit-to-stand, in a patient with bilateral TKR (Rossi *et al*, 2010). A leg-press, involving closed-chain exercise, simulates functional tasks as it allows muscle co-contraction and joint compression without full weight bearing postures that may cause pain and swelling in the initial stage of recovery. Exercise dosage involved three sets of leg-press (30 - 50 repetitions per set) at 40 % -60 % of calculated maximum resistance (1RM) with 30s rest in between sets and progression involving 10 % -15 % increase when programme goals had been become easy to achieve. Results cannot be generalised due to the case-report nature of the study and interesting “hints” regarding volume of exercise and closed-chain exercises resembling functional tasks, should be investigated further in more robust design’ studies. Bade *et al* (2010) also used an intensive strengthening exercise regime in TKR patients and showed that patients recovery to pre-operative levels in terms of pain, quadriceps torque and functional performance was achieved within six months post-TKR.

A combination of quadriceps’ NMES with usual care (ROM, quadriceps strengthening and functional exercises) showed more rapid mid-term (one year) beneficial results in muscle power than isolated rehabilitation in a small sample of patients with bilateral TKR (Stevens *et al*, 2004; Stevens *et al*, 2012). However, treatment volume was not matched between groups. Avramidis *et al* (2003), supported the latter findings when measuring gait speed.

More recently, focus on the addition of elements of balance training to functional exercises programmes has been suggested (Gstoettner *et al*, 2011; Piva *et al*, 2010). Piva *et al* (2010) included adjunct balance exercise within an intensive functional programme, presented in the study by Moffet *et al* 2004 (details in Table 2.2) and found further improvements in gait speed, single leg stability, and stiffness. Therefore, exercises focusing on movements, which are valid for gains in neuromuscular performance and agility, and which perturb the relevant mechanisms and physiological systems regulating their actions, are feasible to be included in patients’ post-TKR conditioning. The exercises will also need to have shown previously the capability for improving knee OA patients’ pain and self-reported functional stability (Ageberg *et al*, 2010; Ageberg *et al*, 2015; Fitzgerald *et al*, 2002). Piva *et al* (2010) provided a detailed description of exercises offered to patients,

accompanied by suggestions on dose and progression during the rehabilitation phase that this thesis will use as the basis for the sensori-motor exercise training programme.

Pre-operative SMT rehabilitation has been shown to improve balance coordination and function in patients with OA before and after TKR, compared to the performance capabilities of age-matched controls (Gstoetnner *et al*, 2011). Therefore, lately the importance of incorporating balance and proprioception exercises within the physiotherapy rehabilitation programme, aiming to improve stability, risk of falls and overall gait and function, is highlighted. The novelty of this type of rehabilitation (as described in section 2.4), is the exposure of patients to movement experiences that challenge knee stability during training in a controlled manner. In this way, the neuromuscular system has been prepared to react rapidly and efficiently to maintain knee stability when the need arises during ADL. The concept of including agility and perturbation training techniques aims to reduce the sensori-motor deficiencies, which are known to occur due to pain avoidance and prolonged inactivity by OA patients. However, since this concept was initially developed to be used in rehabilitation following sports-related injuries, it has to be delivered safely and in a manner that is well-adjusted with ADL, so as to enhance the functional performance of the typical population of TKR patients.

In-home tele-rehabilitation has been recently proposed as equally effective in comparison with home-based or outpatient-based modes of rehabilitation post-TKR, in terms of patients' functional performance (Moffet *et al*, 2015; Toussignat *et al*, 2011; Russel *et al*, 2011). The latter tele-rehabilitation programme comprised of progressive functional exercises delivered twice a week (for one hour), for an eight-week period. Access to high-quality rehabilitation services is not always possible, especially for those who live in rural or remote areas. Therefore, the delivery of an optimum content of exercise training in a home-based environment may potentially be a cost-effective alternative to outpatient-based rehabilitation after hospital discharge, which could potentially be delivered by means of tele-rehabilitation, since it offers equivalent functional gains.

This literature review aimed to set the background and describe the key concepts underlying the context of the main study. The main study (Chapters 8) aimed to

evaluate the clinical effectiveness of usual care practice (functional exercise training) integrated with novel sensori-motor elements that might potentially enhance the clinical care of patients and address persisting deficits that challenge patients' functional performance. This approach took into consideration: i) the implications of dysfunction in the sensori-motor system driven by OA pathology and TKR surgery, ii) the "gaps" within the current literature in TKR rehabilitation care, as well as iii) current novel trends in the rehabilitation care of patients post-TKR. As had been alluded to earlier, it was considered important to explore by means of a clinical survey (Chapter 4), the current clinical practice in Greece for patients undergoing TKR. The survey's findings in conjunction with those from the literature would define what might be considered to be usual care practice and would be used to inform the thesis' main study. Finally, it was considered important to critically evaluate the clinimetric properties of indices used in the literature of patients following TKR. In that way, the selection and justification of which indices would best reflect the outcomes of SMT to inform the thesis' main study could be made (Chapter 3).

Chapter 3

Clinimetrics of indices of functional, balance, sensori-motor neuromuscular, musculoskeletal and psycho-physiological performance of the knee in patients following TKR.

3.1 Introduction

To evaluate the efficacy of any intervention, the outcome measure being used to assess the intervention's impact must possess robust clinimetric and psychometric properties. Knowledge of an outcome measures' clinimetric properties is vital when assessing individualised responses to training after a patient has undergone TKR surgery. The cost of potential falls after TKR can become an immense burden to the health-care provider, with each fall demanding many thousands of pounds in clinical care' costs. Therefore, information from appropriate outcome measures can objectively support the clinical decision about the selection of components of rehabilitative conditioning that may ultimately contribute to patients' enhanced functionality, balance-related performance, and a capability for reducing the likelihood of falling after TKR.

At the moment, there are no guidelines on the best outcome clinimetrics to be used in order to capture patients' level and progress at any stage of recovery following TKR. Therefore, the aim of this chapter is to offer a review of the relevant literature on tools assessing the performance of patients undergoing TKR. For the latter purpose, the clinimetric properties of outcomes used to reflect objective functional, balance, sensori-motor, neuromuscular and musculoskeletal performance, as well as PROMs, will be discussed in order to best select which to use to investigate group-based changes within the main study of the thesis (Chapter 8).

In this section of the thesis, clinimetric utilities (i.e. internal consistency, reproducibility, validity, responsiveness and interpretability) associated with selected PROMs and objectively measured outcomes of functional, balance, sensori-motor, neuromuscular and musculoskeletal performance have been critically appraised in order to determine which outcome measures will be used to best reflect the main study' aims. Minimal detectable change (MDC) and minimally clinically important difference (MCID) have been presented in the relevant outcome measures, when reported in the literature, in order to monitor SMT intervention effects over time and between-groups (main study, Chapter 8), and ultimately, to assure the appropriate interpretation of findings.

Physiotherapists essentially use outcome measures to evaluate and justify good clinical practice. For this purpose, performance-based measures and PROMs that

include the aforementioned measurement' qualities are considered essential in order to assess components of patient' knee-related physical performance. As there is no consensus over the measures used to determine the readiness of physically active patients for a safe return to normal physical activities, any outcome measure that can accurately determine patients' level of functional, postural control and sensori-motor performance would be of highly beneficial and meritorious. Ideally, the tests used should be valid (measure the proper outcome), reproducible (same value should be obtained on repeated assessments of a stable patient), and responsive to changes in patients' condition.

There is strong evidence in the literature to suggest there are deficits in the physical performance of the knee following TKR rehabilitation. At the moment, there are no guidelines on the best outcome clinimetrics to be used in order to capture patients' level and progress at any stage of recovery following TKR. Moreover, the mechanism of action of SMT training has been mostly speculative (please refer to section 2.7, pages 34 - 35). Therefore, before the selection of outcome measures to be potentially used within the research corresponding to the main study of this thesis, can be determined. clinimetric properties of measures already used in the relevant literature have been evaluated.

3.2 Reliability, Reproducibility

The heterogeneity and lack of uniformity in outcome measures applied in arthroplasty rehabilitation suggest little consensus in this field, and make it difficult to generalise findings and to draw conclusions. For example, neuromuscular performance indices such as muscular strength, or peak force synonymously, have been widely reported in the scientific literature to have adequate characteristics of reproducibility and reliability (Gleeson *et al*, 2000; Minshull *et al*, 2007; Minshull *et al*, 2009). However, many other indices related to neuromuscular performance or SMP of the knee joint have received limited scrutiny. The examination of performance capabilities of patients should be undertaken using measurements that are sufficiently precise to facilitate confident discrimination between performances (Gleeson *et al*, 2002).

Measuring tools and procedures are almost always prone to a variety of errors, which ultimately, result in findings that might differ from the true value (Bartlett & Frost, 2008). The presence of some common factors observed during clinical trials such as learning effects, fatigue, insufficient recovery time, motivation, biological or mechanical variation and inconsistency in the measurement protocol, make the outcomes vulnerable in terms of reliability and reproducibility (Coldwells *et al*, 1994). Realistically, some error will be evident within any measuring tool. There are two components of variability associated within each assessment of measurement error. These are systematic bias and random error. Random error or variability is a non-systematic measurement error that is beyond the control of an investigator, though its effects 'average out' over a set of measurements. The heterogeneity in the human population leads to relatively large random variation in clinical trials. The impact of random error can be minimized with averaging over a large number of observations. In contrast, measurement bias, or systematic error refers to deviations that are not due to chance alone and a particular result is favoured (Althubaiti, 2016). A measurement process is biased if it systematically overstates or understates the true value of the measurement. The simplest example occurs with a measuring device that is improperly calibrated so that it consistently overestimates (or underestimates) the measurements. The sum of these components of variation is known as total error (Chatburn, 1996). The reason for having an acceptable reliability is to provide a robust base for the meaningful evaluation and interpretation of the data acquired during research (Hirano & Yamamoto, 2013; Mercer & Gleeson 2002; Minshull *et al*, 2009).

Measurement precision is simply defined as the ability of a performance index to show a consistency of measurement when it repeated using a specific test protocol and under the same environmental conditions (Denegar & Ball, 1993). Achieving precise measurement requires a phase in which habituation takes place for the participant, in order to eliminate systematic and statistically significant changes in performance scores, while maintaining the same experimental conditions. The learning effect is normally indicative of a lack of an adequate habituation phase and could interfere adversely with the proper assessment of measurement precision (Gleeson *et al*, 2002; Minshull *et al*, 2007). A habituation phase therefore allows attributing the changes observed amongst performance measurement (during a

period without any interventional effects occurring) to the biological variation or error within individuals, as opposed to the carry over effects (i.e. learning effect).

Reliability is the degree to which repeated measurements vary for individuals, i.e. the less they vary, the higher the reliability (Bruton *et al*, 2000). The standard error of measurement (SEM), coefficient of variation (CV) and Bland & Altman's 95 % limits of agreement (1986) are all examples of measures of absolute reliability. Reliability testing is usually performed to assess one of the following:

- Instrumental reliability, i.e. the reliability of the measurement device.
- Rater reliability, i.e. the reliability of the rating or perception associated with the researcher/observer/clinician administering the measurement device.
- Response reliability, i.e. the reliability/stability of the variable being measured (Bruton *et al*, 2000).

Reliability can be quantified using the intra-class correlation coefficient (ICC), along with the SEM, in order to quantify and relate variability of the performance capabilities of an individual from within the group to the variability associated with the group as a whole (de Vet *et al*, 2006). Values close to 0 indicate a totally unreliable single measurement, while ICC values close to 1 represent perfect reliability. Another frequently reported estimate of measurement reliability is the SEM, which distinctively defines different properties from the ICC, including the ability to be less influenced by inter-population heterogeneity (Gleeson *et al*, 2002; Minshull *et al*, 2009; Stratford & Goldsmith, 1997). While the ICC reflects a general ability of a measure to discriminate among patients, SEM defines the magnitude of error of the measure being used. However, values of the ICC do not reflect the expected magnitude of measurement error and can, therefore, be difficult to interpret for clinical measurements. Such information is provided by the precision of measures or through reproducibility and repeatability limits, respectively (Mason *et al*, 1989; Altman, 1991). In this situation, reproducibility limits express the limits of variability that can be expected on the difference in independent measurements made on a subject by different testers, and repeatability limits express the limits of variability that can be expected on the difference between repeated, independent measurements made on a subject by the same tester (Mason *et al*, 1989).

Greco *et al* (2010) defined MCID as “the change score that serves as the optimal cut-off point for discriminating individuals who perceive themselves to be improved from those who do not”. Determination of the MCID is important for several reasons, including judging the magnitude of the benefit when comparing two treatments, calculating a sample size, making inferences about the percentage of patients improved by a therapeutic intervention, and making cost-effectiveness comparisons. Obtaining the values of MCID of an assessment tool helps clinicians to understand the confidence with which patients might respond to changes in scoring on the assessment tool used (Reid *et al*, 2007). For example, Roos and Lohmander (2003) investigated the MCID for knee injury and osteoarthritis outcome score (KOOS) and identified that a change score of eight points indicate a clinically significant difference between those who clinically “improved” and those who “did not”. However, an issue arising is the relationship between the MCID and the level of statistical significance when an intervention is applied. It is possible an MCID might be larger than the difference associated with statistical significance, especially a clinical trial involving a large population. Under such circumstances the ‘significant difference’ could be of little practical importance as the situation regarding the individual participant in such a study, or indeed a patient, is unclear. Nevertheless, it should be understood that the MCID is instrument-dependent (Dvir, 2015).

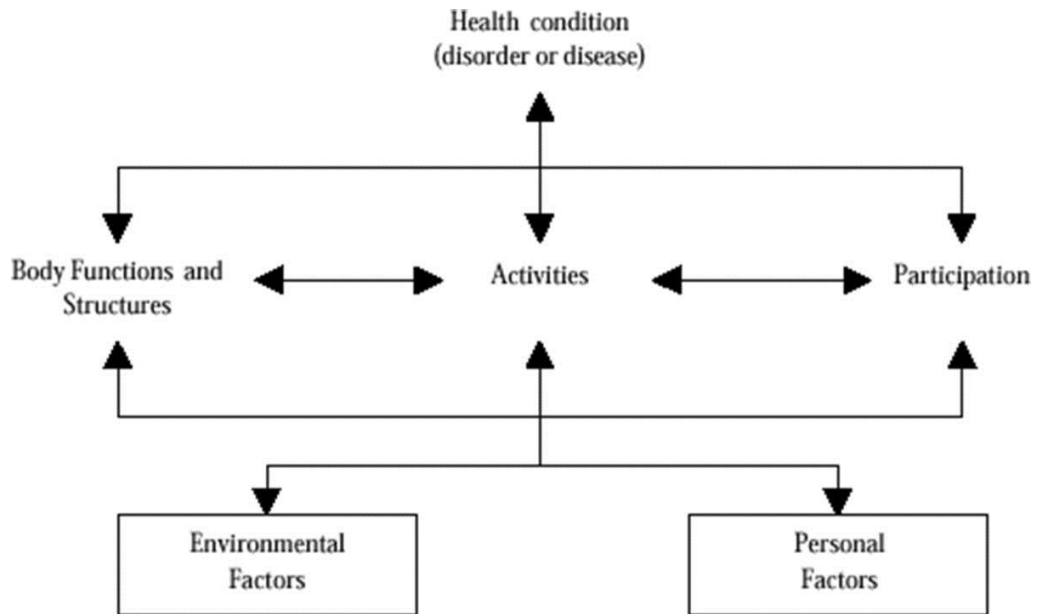
The computation of minimal detectable change (MDC) for a given outcome reflects an estimate of the limits of precision with which it can be measured and as such, it is analogous with other estimates of measurement reproducibility such as the coefficient of variation (Sokal & Rohlf, 1981). One advantage of the MDC is that it considers both the reliability and responsiveness to change. That is, the MDC helps clinicians determine whether the change score in individual performance represents real and reliable change and simultaneously tells whether the outcome measure will be able to detect such a change (Beckerman *et al*, 2004). Measurements of outcomes which exceed MDC’ or corresponding coefficient of variation’ limits during expected longitudinal changes in a patient’s performance, offer confidence of real changes in performance to the level of the specified limits. For normally-distributed error scores, this is often expressed as $\pm 68\%$, or $\pm 95\%$ limits, corresponding to specified conventional extremes of the distribution of errors (e.g. $1 * SD$ and $1.96 * SD$). For individual-level use (i.e. within-person change), the established minimal MCID value should be greater than the MDC to indicate that the measure has

the precision to indicate meaningful clinical change (Wagner *et al*, 2008). In summary, interpretation of the meanings of change scores is a critical issue that should be considered while assessing the usefulness of outcome measures. Determination of the MDC and MCID is critical for judging whether treatments have resulted in real change and the magnitude of the benefit of interventions. In order to have confidence in MCID, multiple measurement replicated across multiple research trials would be needed (Revicki *et al*, 2008). There is no agreed method to calculate MCID and it can really be estimated (Revicki *et al*, 2008).

3.3 Objective functional outcome measures

The World Health Organization has introduced the International Classification of Functioning, Disability and Health (ICF) [International Classification of Functioning, Disability and Health, 2001, World Health Organization, Geneva], which provides a theoretical framework on which to base the assessment of function. As shown in Figure 3.1, this framework splits function into three separate domains: impairment (I), activities limitations (A) and participation restrictions (P). The value of this in the context of TKR can be illustrated by taking the example of climbing a step, a common problem for people considering a TKR. The impairments might include reduced joint movement, pain on movement, and muscle weakness; the resulting activities limitations might be difficulty climbing stairs, and/or difficulty getting onto a bus. Consequent participation restrictions might be inability to get to the shops, or to go to stay with grandchildren because of the expectation of the need for stair-climbing at their home.

Figure 3.1 Framework of function as defined by ICF (adapted from Wylde *et al*, 2012).



A consensus regarding the importance of functional tests following TKR has been reached in the literature (Kennedy *et al*, 2002). However, there are no gold standards in terms of TKR outcome tools. It is believed that these tests assess an individual's ability to respond to physical demands inherent within ADL. Performance-based tests are necessary to fully characterise the change in physical function of patients after TKR, as they provide objective information of how patients actually function, a feature which is not captured by patient-reported outcome measures (PROMs). A variety of tests assessing patients' functional performance post-TKR such as the Timed Up and Go (TUG) Test, 30s chair stand test, stair-climb test (SCT), Six Minute Walk test (6MW) has been reported (Table 3.1). Most tests include the recording of the time taken for patients to perform the requested activity. Despite the fact that a large number of these tests might be useful for assessing the present condition of the knee joint, nevertheless, the use of a reliable and valid functional test is important for clinicians to judge functional capabilities and patient safety.

Table 3.1 Summary of measures used to assess function pre-operatively and post-operatively after joint replacement (adapted from Wylde *et al*, 2012).

Performance tests	ICF domains assessed			Scoring, requirements	Concept	Reliability SEM	and MCID/ MDC
	I	A	P				

Performance tests	ICF domains assessed			Scoring, Concept requirements	Reliability SEM	and MCID/ MDC
	I	A	P			
6 MW	-	++	-	Walking Distance, Exercise capacity motion parameters	ICC = 0.94 (95 % CI: 0.88,0.98); SEM = 26.9 m	MDC = 61.3 m
TUG	-	++	-	Time, Multi-activity-motion parameters. Participants taking > 13.5s to complete the TUG are at increased risk for falls.	ICC= 0.97 (95 % CI: 0.95 – 0.98); SEM=1.07 s	MDC = 2.49s
30 s chair rise test	-	++	-	Completion, motion parameters	ICC = 0.98 (95 % CI: 0.94, 0.99); SEM = 0.7	MDC = 1.6
Stair climb test	-	++	-	Functional strength, balance through a set of steps.	ICC = 0.94; SEM = 1.14	2.6s (11 steps)

ICF= International Classification of Functioning, Disability and Health, I=Impairments, A=Activity limitations, P=Participation restrictions. The extent to which I, A and P is assessed within each tool is indicated using the following symbol system: - no items assessing domain; +/- a small number of items assessing domain; + some items assessing domain; ++ the majority of items assessing domain.

In a systematic review by Terwee *et al* (2006), in examining the measurement properties of all performance-based methods that have been used to measure the physical function of patients undergoing hip or knee replacement, found the TUG Test to have positive ratings for reliability and construct validity. They concluded that multi-activity tests are more valid for measuring the physical function of patients with OA of the hip or knee compared to single-activity tests, such as walking tests, because patients with OA of the hip or knee experience functional problems in more activities than just walking (i.e. climbing stairs or standing up from a chair). A more recent systematic review with a similar purpose, reported the best measurement evidence for the TUG Test and the 30s chair stand test for hip/knee OA (Dobson *et al*, 2012). A longitudinal study by Mizner *et al* (2011) investigating functional

recovery following TKR, used an array of performance-based outcome measures such as TUG, SCT, 6MWT, and showed that these measures are responsive to change and reflect actual activity' limitations of these patients, and to an extent that was more prominent than had been noted for PROMs.

From a practical point of view, apart from the clinimetric properties and the time needed to complete the test (which mostly assesses patients' burden), other requirements such as the extent of apparatus and space required, also need to be considered before the use of an outcome measure is endorsed for clinical or research purposes.

Timed Up and Go Test

The TUG Test requires a patient to rise from a chair (height 42 cm, depth 26 cm), walk three metres at a self-regulated speed, turn, and return to sit down. The TUG Test is one of the simple and quick tests to assess patients' functional mobility. The TUG Test (Podsiadlo & Richardson, 1991) has been extensively used to examine functional outcomes in OA patients and patients post TKR (Finch *et al*, 2002; Kennedy *et al*, 2005). The study by Shumway-Cook & Woolacot-Brauer (2000) has reported that older adults who take longer than 14s to complete the TUG have a high risk of falling. In the literature, patients have exhibited a score of 7.3s, three months after TKR (Yoshida *et al*, 2003). Recently, the Osteoarthritis Research Society International (OARSI) recommended a set of five performance-based tests of physical function, including the TUG Test, for individuals diagnosed with hip or knee OA (Dobson *et al*, 2013).

The TUG Test has been shown to have excellent single-measurement reliability in older adults ($ICC_{2,1} = 0.97$), when assessed in a group of community dwelling elderly people (age range, 61-89 years) (Steffen *et al*, 2002), with a SEM of ~1.1s and was found to be responsive to changes after TKR (Kennedy *et al*, 2005; Podsiadlo & Richardson, 1991). The MDC has been reported as 2.49s in TKR patients, whilst an MDC of over 1.14s in TUG scores has been reported in OA patients (Alghadir *et al*, 2015). The TUG Test has shown good clinimetric properties, and is a time-efficient task that reflects multiple dimensions of ADL (i.e. rising from a chair, balance in standing, walking, turning).

Stair Climbing Test

The Stair Climbing Test measures the time it takes a subject to go up and down a flight of stairs as quickly as they are able, while feeling safe and comfortable (Mizner *et al*, 2005a; Mizner *et al*, 2005b). The clinimetric properties of the test appear in Table 3.1.

6MW

In the six minute walk test, subjects were asked to cover as much distance as possible while walking laps on a 157 m course in a three metre wide hall (Enright *et al*, 2003). The clinimetric properties of the test appear in Table 3.1. The 6WM test is however, a time-consuming test which requires substantial space and measures only the dimension of walking.

Taking into consideration, the aforementioned literature, the TUG Test has been selected as a candidate for inclusion within the main study of this thesis (Chapter 8), as an outcome measure of functional performance, since: a) it encompasses multiple tasks of ADL, b) it is time-efficient, and c) it has been shown to have good clinimetric properties in patients undergoing TKR. A performance-based measure, as opposed to a PROM, would be chosen as the primary outcome because patients with TKR tend to fail to capture acute declines after TKR and overstate the long-term functional improvements with surgery (Mizner *et al*, 2011). Self-reports of physical function are often influenced by pain (Stratford, 2006). Moreover, Norén *et al* (2001) investigated the applicability and reliability of some balance assessment methods, including the TUG Test, in individuals with peripheral arthritis. They reported that the individuals with severe disability were generally able to perform the TUG Test. Therefore, in summary, it seemed reasonable to have chosen on the basis of the evidence from the literature, an objective marker of physical performance, which is also an effective indicator of balance performance and falls risk.

3.4 Clinimetric properties of sophisticated systems to assess balance

Clinical balance assessment can be divided into two main approaches: a functional assessment and a laboratory-system assessment. A functional approach is used to identify whether or not a balance' problem exists in order to assess risk of falls, whereas an approach using laboratory-based system is usually objective and more

accurate. These sophisticated laboratory systems help to identify the constraints or disordered subcomponents underlying control of balance related to biomechanics, motor coordination and sensory organisation. Therefore, determination of the underlying cause of a balance problem in order to design an appropriate treatment programme, may be feasible. Posturography is the quantitative and objective measurement of balance capability that can overcome the main drawbacks to the functional clinical balance examination, such as: i) variability in test performance (within and across different examiners), ii) the subjective nature of the scoring system, and iii) sensitivity to small changes (Visser *et al*, 2008). In addition, quantitative posturography can be used to evaluate therapeutic efficiency, and to predict risk of falls (Pirtola & Era, 2006).

Posturography

Posturography is the general term encompassing all the techniques used to quantify postural control in upright stance, in either static or dynamic conditions, by means of a force platform and the available user-friendly software interfaces for data analysis (Bloem *et al*, 2003). Posturographic analysis on force platforms has been extensively used to assess balance. Force platforms are instruments that measure ground reaction forces generated by a body standing on or moving across them, to quantify biomechanical parameters of human balance control and for the analysis of gait. Force platforms are also used for gait analysis. Posturography allows recording of objective measures of kinetic data (causes of movement related to momentum, weight, force) such as center of pressure (COP), torques, shear forces and moments to characterise human postural sway (Visser *et al*, 2008). For example, a higher mean velocity in the COP movements due to ageing, has been reported.

Static posturography provides linear, objective, and reliable measurements of static balance. Moreover, it evaluates balance control in the most simplistic of conditions, and thus, does not properly reflect scenarios assessing capabilities within ADL. Dynamic posturography, on the other hand, involves the use of experimentally induced (external or self-generated) balance perturbation, such as shifting the support surface, using an unstable support surface, moving the visual surround, applying stimuli to upper body parts, and performing voluntary weight' shifts. By manipulating one or more specific inputs (visual, vestibular, or proprioceptive) for

postural control, a dynamic posturography assessment may provide important data on the motor and sensory contribution to balance control (Furman *et al*, 1993). Thereby, impairments in sensory reweighing and integrating of afferents inputs can be easily detected. Sensitivity to differentiate amongst patients with a balance disorder and healthy individuals, ranged between 57 % and 89 %, and specificity between 88 % and 100 % for dynamic posturography, depending on the criteria used (Goebel *et al*, 1997). There are several types of computerised posturography instruments that are commercially available and therefore, likely to be offering varying levels of technical error to measurement reliability scores. To date, limited studies have a limited number of reported clinimetric comparisons of commercially available computerised instruments. Although dynamic posturography systems provide accurate data about body sway and represent a gold-standard in measuring the motor and sensory contributions to balance control, an important drawback is the high cost, the long time of administration (training and testing), and bulky equipment (Visser *et al*, 2008).

Recently, wearable motion sensors developed for robotics, aerospace and biomedical measurements have been used to measure balance control (Mancini & Horak, 2010). These sensors, with wireless data transfer, have the potential to overcome the major drawbacks of cost, size and limited location of computerised testing, as well as enabling objective measurement of postural sway and movements during task performance. However, these sensor-systems are not yet extensively used in clinical settings.

Biodex Stability system

Biodex Stability System (BSS) (Biodex Medical Systems, Shirley, NY) is one of the quantitative posturography instruments for the assessment of balance and risk of falls. The BSS provides quick and quantitative measures of postural control, center of pressure location, and (indirectly) the overall function of the sensori-motor system. The BSS uses a microprocessor-based actuator to adjust the stability of a suspended circular force plate. The force platform has a maximum of 20degrees of tilt in any direction when completely unstabilised and determines a participant's stability based on the variance of the platform from center during a given task using a sampling rate of 100 Hz. The stability of the BSS platform can be varied by adjusting the level of spring resistance (i.e. support) from one (least stable) to twelve

most stable) (Hinman, 2000; Schmitz & Arnold, 1998). Main outcome measures include the overall stability index (OSI), the anterior/posterior stability index (APSI), and the medial/lateral stability index (MLSI). The OSI represents the total variance of platform displacement (all directions), measured in degrees, with higher scores indicating worse postural control, while the APSI and MLSI represent platform displacement in the sagittal and frontal planes, respectively (Arnold & Schmitz, 1998; Riemer & Wilkstrom, 2010). The following formulas: $OSI = [(\sum(0-Y)^2 + \sum(0-X)^2 / \text{number of samples})]^{0.5}$, $APSI = [(\sum(0-Y)^2 / \text{number of samples})]^{0.5}$, $MLSI = [(\sum(0-X)^2 / \text{number of samples})]^{0.5}$, where Y and X represent the degree of platform tilt in the sagittal and frontal plane, respectively, were used to calculate the outcomes of interest. Among the three indexes, the OSI has been shown to be the most reliable (Cachupe *et al*, 2011; Perreira *et al*, 2008). Numerous papers report high test-re-test reliability for the BSS when using high resistance levels (ICC = 0.7 for dual limb stance and ICC = 0.9 for single limb stance) (Cachupe, *et al*, 2001; Parraca *et al*, 2011; Sherafat *et al*, 2013). However, reliability data for lower stability levels, which are more challenging and dynamic in nature, is scarce within the literature (Cachupe *et al*, 2001). More challenging tasks, such as balancing on a highly unstable surface, have also been associated with more pronounced learning curves (Nordahl *et al*, 2000; Valovich *et al*, 2003). The BSS has high test-re-test reliability when stable (high) resistance levels are used and a SEM of 1.06 degrees (°) of tilt (Cug & Wilkstrom, 2014). The higher MDC scores for the BBS of ~3 degrees (Cug & Wilkstrom, 2014), might be explained by the scores being obtained under conditions involving lower stability levels, which might be associated inherently with greater levels of random measurement error, and which would require greater practice to achieve a stable score for assessments undertaken both within and between test sessions.

In considering candidate outcomes for use within the main study of the thesis (Chapter 8), the BSS was logistically the only available instrument that could have been used for the assessment of balance. In order to achieve high reliability of measurement for the assessment of balance within the main study, a protocol using a single limb stance and a high spring resistance would be adopted, according to the recommendation from the literature (Cug & Wilkstrom, 2014). In addition, consideration would be given to adopting a permitted knee-flexed position within the BSS' protocol, which has been shown to offer greater stability (compared to a

straight-leg position) for balance scores using the OSI ($p < 0.001$) and APSI ($p < 0.05$), but not for the MLSI (*ns*) (Perreira *et al*, 2008).

3.5 Validity and reliability of techniques to measure sensori-motor performance (knee joint position sense and kinaesthesia).

Proprioception acuity encompasses components including joint position sense (JPS), velocity, movement detection and force (Stillman *et al*, 2002). Proprioceptive sensation is derived peripherally from mechanoreceptors located in muscle, tendons, joint capsule, ligaments, and skin, which are stimulated by mechanical deformation. Motion stimulates mechanoreceptors providing proprioceptive sensation required during tasks using every kind of physical demand. Primary afferent fibres innervating muscle spindles provide the principal receptors for limb position sense (please refer to Figure 2.3). Mechanoreceptors in joint capsules and cutaneous tactile receptors may also contribute. Secondary afferent fibres innervating muscle spindles possess little rate sensitivity and thus, provide information only about muscle length and thereby, limb position sense (Gilman, 2002). In case of injury or pathology, the feedback system described in the previous sections, is deranged. The assessment of knee SMP is of paramount importance in order to evaluate patients' functional capability and clinical outcomes of rehabilitation programmes. Different types of joint and muscle disorders may present different deficits for a particular SMP component.

The two measurement techniques that have so far been mostly identified to measure joint sensori-motor performance (proprioception) in clinical settings are: i) assessing threshold to detect passive joint movement (kinaesthesia or motion test sense) and ii) assessing joint position sense (presented in Table 3.2). Despite differences in the methods used to quantify SMP, each attempts to eliminate visual, auditory, vibrational, pressure, or cutaneous tensional feedback within the joint of interest.

Threshold to detect passive motion

Kinaesthesia was measured by the ability to detect the threshold of passive motion (TDPM) through passive slow knee motion (Barrack *et al*, 1983; Koralewitz *et al*, 2000; Lund *et al*, 2008; Pai *et al*, 1997; Sharma *et al*, 1997). Ageberg *et al* (2009) used a specifically designed apparatus (evolved technologically from previous

studies) to measure kinesthesia, where subjects were asked to close their eyes, concentrated on their knee and to respond when they felt sensation of movement in their knee. Motion sense tests are probably mediated by articular mechanoreceptors, especially Ruffini mechanoreceptors, which are mostly stimulated by slow, steady changes in joint position (Simmons *et al*, 1996). This apparatus has been validated in normal subjects and patients following knee ligament injury and surgery (Lephart *et al*, 2002). The test of threshold to detect passive motion (TTDPM) has shown good clinimetric properties (ICC = 0.8; SEM = 1.1 °).

Joint positions sense (JPS)

The assessment of JPS is the most common method to assess knee SMP (Smith *et al*, 2012). This technique involves assessment through either active or passive reproduction of a specific target knee' angle after the joint is returned to its initial position. Active reproduction of joint angles assesses both the muscle and the capsular receptors, whereas passive repositioning primarily measures the capsular receptors. Joint position sense tests probably stimulate both articular and muscle spindle receptors (Bennel *et al*, 2004). Bayramoglu *et al* (2007) used the continuous passive mode of an isokinetic dynamometer to measure reposition error, whilst OA patients wore inflatable boots to preclude any sensational cues. Patients' knee ROM was set from 0 ° to 90 ° and they were asked push the button when they sensed their knee was at 45 ° of flexion. It has been suggested that weight-bearing tests (standing) versus non-weight-bearing (sitting), although more functional, could be influenced by patients' knee pain, muscle weakness and imbalance in standing (Lokhande *et al*, 2013; Marks & Quinney, 1991; Stillman & McMeeken, 2001). Lower repositioning errors have been reported with active repositioning procedures compared to passive ones, and with an intermediate starting position compared with an extreme one (Lohn *et al*, 2000). Active repositioning could be performed either with a specific target angle requiring to be reproduced by the ipsilateral limb or by the contralateral limb. Jan *et al* (2009) used an active repositioning method for assessing JPS, where patients were instructed to extend the knee joint to a target angle selected at random between 0 ° and 90 ° of flexion, to hold that position for 5s, and to then return to the starting angle for 10s, before extending the knee again to match the target angle, as precisely as possible.

In a recent systematic review including 18 studies, four methods of measuring JPS were evaluated (position replication using a model, image recorded angulation, electrogoniometry and dynamometry angle position chair) and showed good intra-rater reliability for the first two methods reported, whilst variable reliability for the latter two in healthy adults. Inter-rater reliability was shown to be good for image-recorded angulation, electrogoniometry and for angular positioning using a dynamometry chair (Smith *et al*, 2012). The majority of the JPS methods used in testing have acceptable intra-rater reliability (ICC > 0.70 or higher; SEM of 2.26 °) (Knoop *et al*, 2011; Smith *et al*, 2012). Due to differences in protocols used for knee JPS measurement (i.e. sitting or standing, passive or active motion, criterion angle, direction of motion or motion velocity), or perhaps due to each protocol measuring a different and thus, unrelated aspect of sensori-motor performance, correlations between methods do not seem to exist (Ageberg *et al*, 2007, Boermboom *et al*, 2008). However, further research has been suggested as being needed to assess whether varying degrees of generalisability and reliability of assessment' methods exist for different knee pathologies.

Knoop *et al* (2011) in their narrative review concluded that position sense tests are measuring capabilities that are closer to the need for SMP in the real-world. However, in order to enhance reliability of procedures for testing, a sitting position should be preferred, non-weight-bearing positions should be used, and the test' angle should be selected with a middle range of joint ROM (40 ° - 80 °). Therefore, in the literature a new measurement protocol has been proposed for development to combine advantages of both methods (tests of position sense and perception of motion) to produce a functionally relevant and reliable outcome measure (Knoop *et al*, 2011).

Table 3.2 Comparison of protocols used in TTDPM, JPS, tests (modified from Han *et al*, 2016)

Variable	TTDPM	JPS
Movement type	Passive	Passive/active
Movement velocity	Very slow	Slow/normal
Practice/familiarisation trial number	Unfixed	Unfixed
Testing trial number	3 - 5 correct answers	Usually 3 - 5, up to ten trials
Movement difference between familiarisation and testing	No	Depends on the types of movement used in target joint position establishment and reproduction

Proprioceptive information	Largely movement information	Depends on whether a physical stop is used during target joint position establishment
General vision	Blocked	Blocked
Audio	Blocked	Available
Posture	Usually lying or sitting	Usually lying or sitting
Constrain	Usually constrained	Usually constrained
Weight-bearing	Usually none or partial weight-bearing	None, partial or normal weight-bearing
Attention requirement	Very high	High
Memory requirement	Very low	High
Measurement	Difference between the start position and responded position	Error between the target position and performed position
Unit	Degree	Degree
Testing duration	Up to 6 h	Depends on the number of trials used
Reliability	ICC=0.8; SEM=1.1 °	ICC>0.7; SEM = 2.3 °
MDC	1.3 °	-

Abbreviations: TTDPM = threshold to detection of passive motion; JPR = joint position reproduction

Recent studies of SMP have focused on achieving rapid, dynamic and ecologically-valid assessments of performance in which the capability for timely, rapid, forceful, precise and efficient responses from the neuromuscular system are gauged against the likely threats arising from within every-day sporting environments (Gleeson, 1999; 2000).

After TKR, the knee joint relies more on active proprioceptors (ligaments and capsule are resected). In summary, an active angle' reproduction method, undertaken in a sitting position, offered sufficient clinimetric quality to be selected for assessing SMP within the main study.

Force error

Recent studies (Gleeson, 2000; Gleeson *et al*, 2008) have piloted the use of a neuromuscular assessment protocol, in which subjects are required to match as precisely as possible, a previously learned 'blind' target force during static knee extension or flexion efforts. The force-time history of the subject's response has been regulated volitionally, but it has generally lasted between 2 and 3s. This allows the subject to regulate 'on-line' motor-unit recruitment and ultimately force, on the basis of sensory (proprioception) information. The subject's best match of the

prescribed target force has been indicated by a voluntary relaxation of the involved musculature that can be easily distinguished by the test administrator subsequently by interrogation of the force-time record.

Based on the literature, there are two main approaches used to measure the sense of force. The first attempts to reproduce a target force as a certain level of maximum voluntary isometric contraction (MVIC) of a muscle group in one limb or a reference side, and is known as the 'ipsilateral remembered method'; the second, aims to reproduce the same target force in the opposite limb, and is known as 'the contralateral method'. Evaluations of sensori-motor capabilities using techniques that require perceptions of force, demand commensurate precision within the device for measuring muscle tension in both limbs simultaneously, or in a rapid sequence.

In order to detect PF, three single, strong voluntary isometric contractions, with 60 s rest intervals, were recorded for knee muscle groups separately. Each verbally prompted contraction lasted for 5s, and the highest value was recorded as the PF. Later, in this type of assessment of SMP, the participants were required to reproduce a blinded prescribed target force that had been selected to be 50 % of their individual capability for maximal voluntary muscle action (at a given angle of joint flexion), and associated with the expression of peak muscle power during dynamic muscular activations, according to force-velocity and power-velocity relationships (Hill, 1938). This approach to the assessment of sensori-motor performance has also been evolved to reflect more closely the corrective muscle actions to a specified and effective target level of force to stabilise a synovial joint under mechanical stress, in a timely manner. A novel development of this approach to the assessment of SMP is the reporting of the participant's self-perception of the extent and the direction of error in the execution of reproducing the target force (Alhajaya, 2005). However, it is noteworthy that there has been no scrutiny of self-perception of the capability for SMP in comparison to objectively assessed capability for sensori-motor performance. The single-measurement reliability (ICC) of the objectively-measured approach ranged from 0.73 to 0.81, with a SEM of 0.4 N and a MDC < 1 N (Zavieh *et al*, 2016) in healthy adults. Force error has been shown to provide clinically useful information of SMP with acceptable clinimetric properties. Thus, it has been selected for use within the thesis' main study to reflect a novel

outcome measure in the TKR population, showing predominantly the 'muscle sense' in controlling quality of motor function (Henningesen *et al*, 1997).

In the current study, participants were routinely required to report to the test administrator, their self-perception of the extent and the direction (positive and negative indicating, whether they believed they had exceeded or fell short of the target, respectively) of error associated with individual trials, during the learning process for the 'blinded' target force. Initially, participants verbalised these self-perceived scores during preliminary trials using the same arbitrary scale of measurement without units used during the learning process. For example, feedback from the participant was required in standardized terminology such as "25 high", "20 high", "15 high", "10 high", "5 high" and "25 low", "20 low", "15 low", "10 low", "5 low", respectively, or "no error", as appropriate. Once the participant had been familiarised with this process of reporting their self-perceived performance outcomes, he/she was required to transfer these reports to a non-verbal, written format in which a series of miniature visual-analogue scales (using the same unit-less scale of points in the range +25 to -25) were marked appropriately after each block of trial.

3.6 Clinimetric properties of indices of voluntary neuromuscular performance.

The fundamental purpose of an index of leg muscle neuromuscular function is to provide a reliable estimate of performance capacity. Within a given measurement setting, suitable reliability characteristics should ensure that the index is sensitive to small changes in performance capacity. Peak force (PF), the speed by which muscle force can be initiated (electromechanical delay), and rate of force development (RFD) rapidity with which meaningful levels of force can be mustered, are all measures reflecting neuromuscular performance. These indices can provide markers of the dynamic capabilities available during mechanical loading of a particular joint system (Gleeson *et al*, 1997; 1998a, b; 2000).

Peak Force of the quadriceps

Although methods of measuring muscle strength vary between studies, reported quadriceps strength deficits range from 15 % to 40 % depending on OA severity.

Quadriceps' weakness is attributed in part to the inability of the CSN to voluntarily activate the muscle. Voluntary muscle activation can be measured by having the participant perform a MVMA. Participants are seated on an isokinetic dynamometer with hips and knees at 90° and the lower limb affixed to the dynamometer arm. After a familiarisation procedure, participants were instructed to extend the leg as fast and forcefully as possible against the resistance offered by the dynamometer's lever-arm. Quadriceps' strength and voluntary activation are important targets of interventions for patients with knee OA, and various measures of strength and voluntary activation are frequently used to evaluate treatment effectiveness. It is therefore imperative to establish the reliability of these measurement techniques and to estimate the minimal level of change that can be detected confidently between test sessions.

Excellent test-re-test reliability (ICC > 0.98; SEM ~10.8 N) has been reported for isometric strength measures in patients with knee OA. The MDC at a 90% confidence level, for quadriceps' isometric strength was 25.0 N, which equated to a performance change of ~ 15 % compared to the group mean baseline score (Kean *et al*, 2010). Methodologically diverse investigations have examined the reproducibility of peak force of the thigh musculature subsequent to volitional muscle activation and have reported intra-day coefficients of variation (CV %) of 4.1 % (Viitsalo *et al*, 1980).

The index of PF was selected as a marker of physiological capability associated with voluntary forceful activation of the knee joint extensors inherent in many activities of daily living, with good clinimetric properties.

EMG-derived measures

The surface electromyography (EMG) method provides easy access to the physiological process that causes the muscle to generate force, produce movement and accomplish the essential functions of every days live (De Luca, 1997). Raw EMG data can be processed in a number of ways to compute a variety of parameters to quantify the neuromuscular status of a given muscle. In the time domain, peak amplitude and root mean square (RMS) have all been described in the literature (Dimitrova & Dimitrov, 2003). In the frequency domain, median power frequency (MPF) is commonly used for evaluating fatigue (Ament *et al*, 1996). The

relevance of these variables has been justified by literature regarding static and dynamic contractions (Rodríguez & Agre, 1991; Giroux & Lamontagne, 1990).

Peak Amplitude

It is well known that the amplitude of the EMG signal is related to the strength that a muscle can produce. Narici *et al* (1989) and Sbriccoli *et al* (2003), observed a linear correlation between the values of the amplitude of the EMG signal and the isometric strength of muscles such as the biceps brachii, the vastus lateralis, among others. Recording the EMG signal during maximum and submaximum isometric actions of the knee extensors is commonly used in the literature as an indirect measure of relevant muscle strength. Once the amplitude of the EMG signal is determined by the frequency of muscular activation and by the number of recruited motor units, the increase in the amplitude of the EMG signal after training might suggest the existence of neural adaptations occurred with the training (Hakkinen *et al*, 2000). Some indices of neuromuscular performance such as peak force (strength) have received extensive scrutiny in the scientific literature for their characteristics of reproducibility and reliability (Gleeson & Mercer, 1992; Gleeson & Mercer, 1996; Gleeson, *et al*, 2002; Wyse, Mercer and Gleeson, 1994). The variability of intra-session estimates of neuromuscular performance is frequently less than that associated with inter-day comparisons (Gleeson & Mercer, 1992) and as such, calculation of reliability based principally on intra-session measures may overestimate the available precision of measurement and fail to account fully for the biological variability inherent in between-day neuromuscular performance assessments (Gleeson *et al*, 2002).

For assessment purposes, patients are placed and restrained on an isokinetic dynamometer usually in a sitting position, and simultaneous EMG activity of the quadriceps muscle is recorded during patients' isometric contraction performance. Bamman *et al* (1997) observed high ICCs between EMG values obtained among five days (ICC = 0.7 to 0.9), in three superficial quadriceps muscles: rectus femoris, vastus medialis and vastus lateralis. Vitsalo & Komi (1975) showed similar values (ICC = 0.8 to 0.9) in the rectus femoris; however, they observed higher reproducibility of measurements within the test session than measurements undertaken on different days. It is well established that EMG activity of knee

extensors is highly reliable during contractions close to MVMA (ICC >0.80) (McKenzie *et al*, 2010; Vitsalo & Komi, 1975).

Root Mean Square Among the EMG-analysed parameters the root mean square (RMS) is considered to be the most sensible and reliable, as it is not affected by the cancellation due to the motor unit action potential train superposition (Basmajian & De Luca, 1985). The RMS value has been used to quantify the electric signal because it reflects the physiological activity in the motor unit during contraction. The square root of the total power yields the total intensity, which is a measure of the time-dependent overall EMG intensity. For RMS processing, the EMG signal is submitted to mathematical treatments that are designed to quantify the intensity and the duration of several events of the EMG signal. A linear relationship with the required torque has been found between the contraction force and the RMS value of the EMG signal in females for the rectus femoris muscle (Fujuda *et al*, 2010). The reliability for RMS has been reported as $ICC_{2,1} = 0.7$ and $SEM = 0.06$. The RMS value is, therefore, a parameter frequently chosen because it reflects the level of the physiological activities in the motor unit during contraction. EMG recorded from the rectus femoris muscle was more reliable than those recorded from the vastus lateralis or vastus medialis (Kollmitzer *et al*, 1999).

Frequency

The EMG frequency spectrum is changed by physiological processes such as fatigue (Basmajian & De Luca, 1985; De Luca, 1997), recovery processes (Rodriquez & Agre, 1991), fibre type distribution and fibre type characteristics (Stalberg *et al*, 1989), and for identification of muscle impairments due to pain (De Luca, 1993). A study by Kollmitzer *et al*, (1999) has shown the quadriceps muscles to exhibit excellent repeatability in MF measurements. There was a remarkably high within day correlation (0.80 - 0.99), but only a moderate reliability between days (0.49 - 0.61).

Rate of force development (RFD) and Electromechanical delay (EMD)

When EMG and isokinetic dynamometry are synchronised it is possible to determine EMD, which refers to the time lag between the onset of electrical activity and force production (Li & Baum, 2004). Rate of force development refers to the rate at which

force can be produced, which is thought to be affected by muscle strength and the muscle tendon complex, both of which are potentially impaired in knee OA. The index of RFD has been determined as the average rate of force increase associated with the force-time response between 25 % and 75 % of PF and calculated for 3 intra-session maximal voluntary muscle actions of the knee extensors. The ICC and associated SEM (95 % CI) for the knee extensors have been found as 0.91 and 42.2 % respectively (Gleeson *et al*, 2002; Minshull *et al*, 2009). Therefore, a limited capability of RFD to discriminate subtle changes in performance-based on a single trial assessment. Electromechanical delay refers to the time required for the series elastic component to take up the slack of the surrounding tissue prior to stretching the series elastic component and force being produced. The time required to stretch the series elastic component may be affected by muscle dysfunction and joint laxity potentially elongating EMD. EMD was defined as the time between the onset of EMG and onset of force. Electromechanical delay has received less scrutiny. A wide range of absolute EMD values reported in the literature for the same muscle has been interpreted by some researchers to represent an inherent variability of this index (Bochdansky *et al*, 2000). This is despite reports of good intra-day reliability ($r = 0.93$ (Vitsalo *et al*, 1980), reasonable measurement reproducibility (CV %: 6.1 % (Gleeson *et al*, 1998b) and the likelihood that diverse methodologies may have differentially influenced the magnitude of EMD scores. No difference in EMD between knee OA patients and age/sex-matched controls. however RFD was impaired in individuals with knee OA (Smith *et al*, 2016). Increased pain has been found to be associated with shorter EMD in knee OA (Smith *et al*, 2016). Although RFD and EMD provide clinically meaningful indices, unfortunately due to lack of relevant technical staff to achieve synchronisation of the EMG equipment the dynamometer, these indices were not included in the main study (Chapter 8).

Overall, EMG measurement at the quadriceps muscle is a reliable method if the following recommendations are taken:

- Isometric contractions
- Reliable and stable positioning of leg and electrodes
- Follow-up interval as short as possible
- Signals preferably taken from rectus femoris

3.7 Reliability of the rectus femoris muscle cross-sectional area' measurements by ultrasonography

Skeletal muscles can adapt to external stimuli arising from either physiological or pathological conditions. Ultrasound has proven to be an effective method for analysis of some parameters of muscle architecture of large muscles, such as the rectus femoris, with the potential to determine the response to training, ageing or disuse (Reeves *et al*, 2004). This plasticity is measured by various imaging techniques such as magnetic resonance imaging (MRI) or ultrasound. The anatomical cross-sectional area (CSA) of a muscle is one of the muscle's architecture parameters that relates to the capacity for maximum muscle strength. Specifically for anatomical CSA, computed tomography (CT) and MRI are considered the gold standards of measurement (Bembem, 2002; Reeves *et al*, 2004; Mathur *et al*, 2008; Seymour *et al*, 2009), but have some disadvantages. The high expense and cumbersome nature of these techniques has stimulated interest in ultrasonography (Seymour *et al*, 2009; Thomaes *et al*, 2007; de Bruin *et al*, 1999). Ultrasound has gained importance as a reliable and inexpensive instrument of measurement to obtain images of muscle tissue (Bembem, 2002), particularly of locomotor muscles (Puthuchearry *et al*, 2014; Noorkoiv *et al*, 2010). Real-time ultrasound stands for its utility by facilitating the two-dimensional analysis necessary to identify the anatomical CSA, while at the same time offering a high correlation with the other imaging techniques (Reeves *et al*, 2004).

The reliability of measurements derived from images by ultrasound involves, beyond the limits of resolution of the instrument, depends on the examiner's experience and accuracy in identifying anatomical sites (Blazevich *et al*, 2006). In this scenario, the ICCs ranged from 0.87 to 0.99 for intra-rater reliability in studies measuring rectus femoris CSA with a corresponding coefficient of variation (CV %) within the range from 3.5 % to 8.9 % (Bembem, 2002; Lima *et al*, 2012). Potential sources of error for this measurement technique have been highlighted as a lack of sufficient muscle relaxation, skin press' variability with the ultrasound probe, participation in physical activity in close temporal proximity to the measurement' occasion. Therefore, ultrasound imaging was selected for use within the main study of the thesis (Chapter 8), as a reliable method to evaluate potential responses of the rectus femoris muscle to training.

3.8 Clinimetric properties of patient-reported outcome measures (PROMs)

It is evident from the literature that patients' satisfaction and the way in which patients perceive the outcomes of a treatment, including perceptions of their functional capabilities, has become very important to clinicians (Jette, 1989). Both PROMs and performance-based measures of physical function are used to evaluate outcomes after TKR. Patient-reported measures are the most commonly used because they are less expensive, are less time-intensive, and reduce the number of patients lost at follow-up because they do not require a clinical visit. The inclusion of PROMs in routine clinical care has been shown to add valuable information, as they indicate the impact of a disease and/or a treatment, and promote self-management of patient care. Moreover, physical performance on individual tasks does not capture functional capacity across a full range of relevant tasks, and performance is not assessed in a natural environment (Gandhi *et al*, 2009, Stratford *et al*, 2006, 2009). In addition, the performance of specific standardised tasks does not necessarily tap into the activities that the individual considers of greatest importance and significance. Thus, performance-based measures also have important limitations. Because performance-based and PROMs tap into different perspectives related to function, a combination of these two approaches are suggested to measure function after TKR (Gandhi *et al*, 2009; Kennedy *et al* 2002; Stratford *et al*, 2006). However, controversies associated with clinimetric utilities of PROMs used for the evaluation of the knee functional performance following TKR, have resulted in the development of different scales.

Clinimetric properties of Numeric Pain Rating Scale (NPRS)

The NPRS is a unidimensional measure of pain intensity in adults, including those with chronic pain due to rheumatic diseases (Hawker *et al*, 2011). The NPRS is a segmented numeric version of the visual analog scale (VAS) in which a respondent selects a whole number (0 - 10 cm) that best reflects the intensity of his or her pain. The common format is a horizontal line. An 11-point numeric scale is administered with 0 representing one pain extreme (e.g., "no pain") and 10 representing the other pain extreme (e.g. "worst pain imaginable"). The number that the respondent indicates on the scale to rate their pain intensity, is recorded. Patients with chronic pain prefer the NPRS over other measures of pain intensity, including the pain VAS, due to its comprehensibility and ease of completion. High test-re-test single-measurement reliability has been observed in both literate and illiterate patients with

RA (ICC > 0.95) before and after medical consultation. In clinical trials of OA, analyses of the relationships between changes in NPRS scores and patient reports of overall improvement, demonstrated a reduction of 2 cm on the NPRS scale (equivalent to a change of 20 %) to be clinically important (Farrar *et al*, 2001). By converting the changes on the NPRS to percentages directly, Sloman *et al* (2006) reported a reduction in pain response of 28.6 % to be a MCID during post-orthopedic surgery assessments.

Clinimetric properties of PROMs reflecting functional and psycho-physiological performance

Patient-reported measures of knee function are important for the comprehensive assessment of rheumatology conditions in both clinical and research contexts. Measures of knee function that assess aspects considered important by adult patients with knee problems such as injury or osteoarthritis (OA). Dimensions deemed to be important to patients included pain, function, quality of life, and activity level. For assessing patients' responses to TKR, frequently-used and validated outcome tools include those that are disease-specific (i.e. WOMAC, Oxford-12), focused on global health (i.e. SF-36, SF-12), or on perceptions on functional capacity (i.e. knee injury and osteoarthritis outcome score, KOOS). The KOOS is based on the WOMAC score but has been expanded to include the outcomes of pain, activities of daily living, sport and recreation function, and knee-related QoL. Other functional outcomes of interest include the International Knee Documentation Committee inventory (IKDC), and the Lower Extremity Functional Scale (LEFS).

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The WOMAC is designed to assess the course of disease or response to treatment in patients with knee or hip OA. It includes three subscales: 1) pain severity during various positions or movements, 2) severity of joint stiffness, and 3) difficulty performing daily functional activities. Studies have generally reported adequate internal consistency for the pain subscale, although there have been reports slightly lower than adequate. There have been mixed findings regarding adequacy of test–retest reliability in knee OA for all subscales (ICC: 0.75 - 0.98). Test–retest reliability for the stiffness subscale may not be adequate for use in individuals with knee OA (ICC: 0.65 - 0.98). Apart from the lower clinimetric properties in the knee OA

population, WOMAC, has not been cross-culturally adapted in the Greek language and was therefore not available for use in the thesis' main study.

The International Knee Documentation Committee (IKDC)

The IKDC subjective evaluation form is designed to detect improvement or deterioration in symptoms, function, and sports activities due to knee impairment. The possible score ranges from 0 – 100, where 100 = no limitation with daily or sporting activities and the absence of symptoms. Test–retest reliability is adequate for groups of patients with knee injuries and mixed pathologies and individuals with knee injuries (ICC: 0.90 - 0.95). However, test-retest reliability is slightly below adequate for individuals who fall into a broader category of knee pathologies (ICC: 0.87 - 0.99). The minimal detectable change has been reported to be between 8.8 and 15.6, and the SEM between 3.2 and 5.6 (Collins *et al*, 2011). The IKDC has been found mostly suitable for patients with a variety of knee conditions, including ligament injuries, meniscal injuries, articular cartilage lesions, and patellofemoral pain and was therefore was not considered as useful in the TKR population.

Knee injury and osteoarthritis outcome score (KOOS) (Appendix VI)

Roos *et al* (1998) developed the KOOS to assess knee joint function, based upon patients' perceptions of capability, but which did not involve an administrator to aid in its completion. This tool is the most popular in studies examining several self-reported aspects of pain, function, and ADL. The content validity of the questionnaire has been justified by including items from the WOMAC score. The KOOS seems to be the main preference of researchers and clinicians for evaluating the outcome of TKR (Escobar *et al*, 2007; Hamel *et al*, 2008; Roos *et al*, 2003).

The KOOS instrument comprises of 42-items within five distinct subscales; pain (9), symptoms (7), ADL (17), QoL related to the knee (4), and sports and recreation function (Sports/Rec) (5). The Likert-version delivers five levels of answers for each item, which are scored from 0 to 4. The aggregate score of each of its subscales is calculated separately, with lower scores indicating lower performance capabilities for functioning in these areas. A detailed overview of how to score KOOS can be found in the study by ROOS *et al* (1998).

Formulas used to calculate scores for each subscale of KOOS:

$$1. \text{ PAIN} \quad 100 - \frac{\text{Mean Score (P1-P9)} \times 100}{4} = \text{KOOS Pain}$$

$$2. \text{ SYMPTOMS} \quad 100 - \frac{\text{Mean Score (S1-S7)} \times 100}{4} = \text{KOOS Symptoms}$$

$$3. \text{ ADL} \quad 100 - \frac{\text{Mean Score (A1-A17)} \times 100}{4} = \text{KOOS ADL}$$

$$4. \text{ SPORT/REC} \quad 100 - \frac{\text{Mean Score (SP1-SP5)} \times 100}{4} = \text{KOOS Sport/Rec}$$

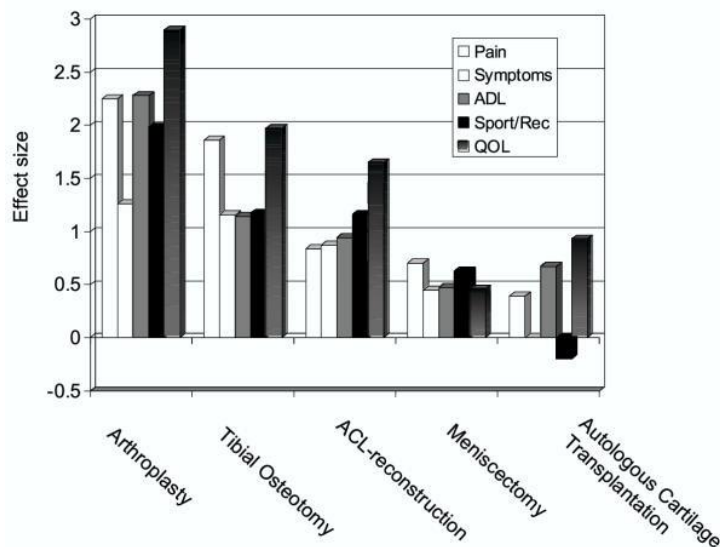
$$5. \text{ QOL} \quad 100 - \frac{\text{Mean Score (Q1-Q4)} \times 100}{4} = \text{KOOS QOL}$$

The KOOS has been validated in many different languages such as English (Roos *et al*, 1998a), Swedish (Roos *et al*, 1998b), Chinese (Xie *et al*, 2006), French (Ornetii *et al*, 2008), Japanese (Nakamura *et al*, 2011), Greek (Moutzouri *et al*, 2014), Persian, Dutch (De Groot, *et al*, 2008) and Portuguese (Goncalves *et al*, 2009). This instrument allows the determination of the changes of function and symptoms that may occur in the knee joint over time. The QoL subscale followed by Pain are the most responsive, having the highest effect size' responses in patients undergoing TKR (Roos & Toksvig-Larsen, 2003), as illustrated in Figure 3.2. Table 3.3 represents internal consistency, test-re-retest reliability, effect size and MDC for each of the five subscales within the KOOS. High response rates, illustrating robust patient-tolerance to the KOOS, have been reported for studies of TKR in the short term: 92 % at six months and 86 % at twelve months (Peer & Lane, 2013).

Table 3.3 The internal consistency, test-re-retest reliability, effect size and minimal detectable change for each of the 5 subscales within the KOOS (adapted from Irrgang *et al*, 2012).

	Symptoms	Pain	ADL	Sports	QOL
Internal consistency	$\alpha = 0.25 - 0.83$	$\alpha = 0.65 - 0.94$	$\alpha = 0.78 - 0.97$	$\alpha = 0.84 - 0.98$	$\alpha = 0.64 - 0.90$
Test-retest reliability	$R_{1-} 0.74 - 0.95$	$R_{1-} 0.80 - 0.92$	$R_{1-} 0.73 - 0.94$	$R_{1-} 0.45 - 0.89$	$R_{1-} 0.60 - 0.95$
Effect Size	0.72 – 1.63	0.82 – 2.59	0.67 – 2.25	0.90 – 1.31	1.15 – 2.8
Minimal Detectable Change	9.9 – 24.3	11.8 – 29.0	11.9 – 31.5	12.2 70.0	14.2 – 34.0

Figure 3.2 KOOS' effect sizes six months following surgical knee interventions (adapted from Roos & Toksvig-Larsen, 2003).



The KOOS has been shown to be a valid inventory in assessing knee conditions, including knee OA. Validity and test-re-test reliability ($ICC > 0.7$) of the KOOS was reported for the subscales of pain, symptoms, ADL, Sports/Rec, QoL in patients with knee OA after TKR (Roos & Toksvig-Larsen, 2003).

Lower Extremity Functional Scale (LEFS)

The LEFS is a 20-item self-reported measure of lower-extremity functional status. It includes items that assess the disablement concepts of functional limitation (activity limitation) and disability (participation restriction). Each item is scored on a 5-point

scale (0–4). Accordingly, total LEFS scores can vary from 0 to 80 points, with higher scores being associated with greater levels of functional status. The test-retest reliability estimate (intraclass correlation coefficient, type 2,1) for the LEFS derived from a sample of patients following arthroplasty was $ICC_{2,1} = 0.85$, the SEM was 3.7 LEFS points, and the MDC at the 90 % confidence level was estimated to be 9 LEFS points (Binkley *et al*, 1999). The LEFS has been found useful for clinicians to make prognoses concerning the rate of improvement in functional status after TKR (Kennedy *et al*, 2008).

Knee Outcome Survey – Activities of Daily Living Scale (KOS-ADL) (Appendix VII)

The KOS-ADL is a fourteen-item self-reported questionnaire to assess how knee' symptoms and knee' condition affects a patient's ability to perform daily physical functions over time (Irrgang *et al*, 1998). The KOS-ADL is represented as a percentage score, with higher scores indicating higher levels of self-perceived functional ability. The KOS-ADL has been shown to have high reliability (0.94 - 0.98) and validity in patients with knee pathology (Irrgang *et al*, 1998). It has been previously used to report patients' self-reported knee-specific functional performance after TKR (Yoshida *et al*, 2003; Zeni & Synder-Mackler, 2010). The MDC in patients with mixed knee pathologies has been reported as 11.5 units and the MCID as 7.1 in patients with patellofemoral pain syndrome (Collins *et al*, 2015; Irrgang *et al*, 1998).

The KOOS and KOS-ADL were selected to assess patient-reported functional performance within the thesis' main study, since both inventories have been shown to have good clinimetric properties in patients undergoing TKR, and because both had been adapted to be delivered with validity in the Greek language (Kapreli *et al*, 2010; Moutzouri *et al*, 2014). LEFS presented with inferior clinimetric properties compared to KOS-ADL and was not available in the Greek language at the time of patient recruitment of the thesis' main study.

12-item Short Form Health Survey Questionnaire (SF-12) (Appendix VIII)

The SF-12 provides a health status profile for measuring eight domains: physical function, pain, general health, social health, vitality, role physical emotional and mental health (Ware & Sherbourne, 1992). It has been widely used as a generic health-related QoL measure in patients undergoing TKR (Escobar *et al*, 2007;

Cushnaghan *et al*, 2009). Knee pain has been found to negatively impact on physical aspects of health-related QoL (Agaliotis *et al*, 2013). The Physical and Mental Health Component Scores (PCS & MCS) derived from the SF-12 are computed using the scores of twelve questions and range from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health. Subjects with frequent bilateral or unilateral knee pain also scored low on the KOOS QoL subscale and the PCS of the SF-12 compared with those without knee pain. Low SF-12 PCS scores among patients with frequent knee pain are indicators of considerable physical limitations, disability, and poorer QoL (Bindawas *et al*, 2015). The MDC for the physical component has been found to be 9.7 units, whereas for the mental component, it has been estimated as 8.0 units (Impellizari *et al*, 2011). All questionnaires used in the study have followed the norms for trans-cultural adaptation and validation (Beaton *et al*, 2000). SF-12 has been adapted and validated to the Greek language (Kontodimopoulos *et al*, 2007).

The current literature review has chosen to include more than one outcome measures for knee function, from both performance-based (TUG) and patient-reported (KOOS, KOS-ADL) in approaches to its assessment in order to assess the merit of each outcome measure. However, this review was not extensive as a systematic review could have been in giving a clear overview of all evidence important quality aspects of outcome measurement instruments and helping to identify the most suitable outcomes for a study, according to COSMIN checklist. The selection for potential inclusion within the thesis' main study (Chapter 8) as assessors of group-based changes, of a battery of indices of functional, balance (BSS System, Postural stability), sensori-motor (JPE), neuromuscular (PF, EMG-derived measures) and musculoskeletal (muscle CSA) outcome measures was firstly performed on the basis of clinimetrics (reproducibility [precision and MDC] and reliability) and responsiveness as estimated by MCID reported in the relevant literature. A further inevitable and important consideration alongside issues of measurement clinimetrics, would be the limited availability of relevant equipment for objective assessments of patients in particular, within the hospital environment. The selection of candidate PROMs was based on their common use in the literature and their corresponding clinimetric properties. The proposed selection of sensori-motor and musculoskeletal outcome measures was relatively novel to TKR patients

and outcome measures were selected in order to obtain a holistic view of patients' recovery procedures and responsiveness inherent within the FET and novel ESMET conditioning that ultimately, would be delivered and compared in the main study. Moreover, the neurophysiological or morphological mechanisms that might underpin any potential effects from the FET and ESMET conditioning programmes would be capable of being assessed by means of a relevant and clinimetrically-competent selection of the representative outcome measures. Knowledge of the quantity of error or precision inherent in each candidate outcome measure and corresponding confidence in detecting particular sizes of performance changes (effect sizes) in patients would be helpful to contextualise their potential utility in counteracting Type-II error rates within a group-based experimental design, such as that in the main study (Chapter 8). Of equal importance however, is that each outcome measure's clinimetric characteristics of reproducibility and reliability will permit informed discussion of its capability for having clinical impact, with a corresponding focus on its limits to being able to confidently detect rehabilitative conditioning-related changes in performance capability of individual patients.

Having reviewed the relevant literature, the outcome measures that were candidates for use, and ultimately deployed within the main study of the thesis, have been determined on the basis of their clinimetric properties, and in conjunction with consideration of logistics of time and equipment availability. As the primary outcome measure, the TUG Test has been selected to reflect group-based changes in patients' functional mobility and balance performance. Moreover, it was decided to include more than one outcome measure of knee function, with both performance-based (TUG) and patient-reported (KOOS, KOS-ADL) types used in order to assess the merit of each outcome measure. The selection of a battery of indices of functional, balance (BSS System, Postural stability), sensori-motor (JPE), neuromuscular (PF) and musculoskeletal (muscle CSA) outcome measures was based on the reasoning of capturing all potential responses to SMT.

Chapter 4

Greek physiotherapists' perspectives on rehabilitation following total knee replacement: A descriptive survey.

Abstract

Background and Purpose: In Greece, as in many countries, there is a scarcity of evidence about the type of physiotherapy services offered for the rehabilitation of TKR. Despite the number of TKRs performed annually in Greece (over 10,000), there are no available clinical guidelines as to the content of best physiotherapy practice. The aim of this nationwide survey undertaken by physiotherapists treating TKR patients post-operatively, was to record standard practice and services available in Greece.

Methods: National survey: Two samples were used from 10 % of public hospitals and 10 % of registered private physiotherapists working in public/private sectors were recruited. The developed survey comprised of questions regarding therapists' profiles and protocols implemented at different stages of rehabilitation and the aims and modalities used.

Results: A 58.7 % response rate was achieved, where 36 % (47/132) of respondents were treating patients in the inpatient phase and 64 % (85/132) after hospital discharge. Patients in Greece are discharged with a home-based exercise programme (56.7 %) and, to a lesser extent, are referred to rehabilitation centres (13.3 %). Strengthening, range of movement and functionality seemed to be the primary goals, especially in the inpatient phase, whereas in the outpatient phase, apart from the larger differences identified, functionality and balance training were more frequently reported.

Conclusions: No significant variations in practice were found during inpatient rehabilitation, whilst there seemed to be diversity across outpatient physiotherapy programmes. The primary focus of physiotherapy programmes seemed to be knee ROM and muscle strengthening. Patients are presented to be mostly discharged from hospital at home with advice and exercise programmes. The current survey suggests that patients' general health and psychological and behavioral issues are the criteria by which physiotherapists select the volume of implemented exercise and progression. However, no specific guidelines were followed.

4.1 Introduction

Recovery after TKR has generally shown consistent improvements in joint' pain, but with variations in functional capability during the first year (Callahan *et al*, 1994; Hartley *et al* 2002; Naylor *et al*, 2009; Kauppila *et al*, 2011). The quality of post-operative care and rehabilitation strategies has been suggested amongst other factors such as pre-operative functional status, age and other comorbidities (Fortin *et al*, 2002; Jones *et al*, 2008; Lingard *et al*, 2004), to be key determinants of the time-frame of recovery, function and quality of life (QoL) achieved by patients (Roos, 2003). Whilst physiotherapy rehabilitation in the inpatient phase has traditionally focused on exercises addressing pain, strength, range of movement (ROM), and gait re-education (Worland *et al*, 1998; Codine *et al*, 2004; Moffet *et al*, 2004; Dauty *et al*, 2007), there is evidence to support the use of accelerated rehabilitation focusing on functionality and patient mobility during the patients' time in hospital (Minns-Lowe *et al*, 2007; Johnson *et al*, 2010; Olmeadow *et al*, 2002; Thomas, 2003; Isaac *et al*, 2007; Cook *et al*, 2008; Klika *et al*, 2009). The only clinical guidelines existing are published in Scotland and suggest that physiotherapy should focus on normal daily activities, ROM and muscle strength for the first three months (Learmont, 2000). Thus, it is likely that considerable practice variation exists during both the acute and post-acute period (Roos, 2003). After hospital discharge, the literature suggests that intensive protocols with emphasis on function, provide the most effective benefits for patients' functional ability (Frost *et al*, 2002; Moffet *et al*, 2004).

Evidence for the type of services offered and the content of physiotherapy practice remains scarce within Greece, as in many other countries. This is the case despite the consistently increasing number of TKRs. The number of TKRs is estimated to be approximately 10,000 per annum in Greece (at a cost of about 7,000 euro per surgery), and reflecting an increase of 150% of the number from 1995 to 2005 (Xreos Zois, 2009). At the same time, while there is no consensus about optimal treatment, there is some evidence in the literature on the type and mode of exercise during TKR rehabilitation that could enhance physiotherapy practice and patients' outcome. It is therefore considered important to record how physiotherapy services work in Greece in order to promote clinical effectiveness and cost-utility strategies. Information about current physiotherapy practice following TKR is needed in order to

know what is done and to develop strategies for increasing the use of evidence-based practice.

Thus, the aim of this study was to describe the standard (usual) care of patients after TKR in Greece, by analysing qualitatively the Greek physiotherapists' perspectives involved in the recovery after TKR. It is hoped that this review will establish a platform of the available contemporary usual care of TKR rehabilitation and potentially offer information on the selected dosage of exercise prescribed. Rehabilitation care after TKR is offered within both inpatient and outpatient services. Following the findings of that survey, and the findings from relevant international literature, what is considered as usual care practice, the timeline and environment of rehabilitation will be established. This will ultimately help to support the design of a pragmatic, standardised usual care rehabilitation programme for patients following TKR. This will also help to inform the next stage of research within the thesis involving its primary aim of (Chapter 8: What are the effects of enhanced sensori-motor exercise training on indices of functional, balance and sensori-motor performance compared to functional exercise training (usual care) in patients following total knee replacement?). This approach would also facilitate the identification of areas of diversity and ambiguity within physiotherapy practice needing further research.

4.2 Methods

Approval from the study was granted by the Panhellenic Physical Therapy Association (PPTA) Research Committee, the official body representing chartered physiotherapists in Greece.

4.2.1 Sample

This sample was a cohort selected using a randomised sampling approach from both inpatient and outpatient physiotherapy practice within Greece. Physiotherapists registered in the PPTA registry (the official body of registered physiotherapists within Greece, working either in the inpatient or outpatient departments in Greece) were eligible for the survey. Exclusion criteria were treating less than ten TKR patients annually and physiotherapists who were not registered in the PPTA registry. Because no official specialties are reported among physiotherapists in Greece (Billis *et al*, 2010), physiotherapists tend to have a relatively broad caseload. Therefore, in

order to achieve physiotherapy' respondents being a representative sample of physiotherapists treating regularly patients following TKR in their routine clinical practice, a minimum of ten TKR patients annually was considered as the borderline for inclusion in the study.

For the inpatient component, randomisation took place in the hospital selection, from where physiotherapists were recruited. In particular, 111 national hospitals with orthopaedic clinics were identified from the Greek Medical Directory for Orthopaedic clinics (Hellenic Association of Orthopaedic Surgery & Traumatology, 2012). In order to obtain a representative sample of Greek physiotherapists from those hospitals, 10 % (eleven public hospitals) were randomly selected. In order to obtain full geographical coverage, a stratified sampling procedure took place, in which Greece was divided into two urban areas (Athens and Thessaloniki) representing the two biggest cities in Greece and four rural areas. Six geographical areas (north, north-west, north-east, central, south-east and south-west) and hospital(s) from each geographical region were randomly (via Microsoft Excel random number generator) selected according to the number of hospitals allocated in each region. Thus, two hospitals were randomly selected from the north, one from the north-west, one from the north-east, four from the central, one from the south-east and two from the south-west regions. Two of the hospitals (one in the north-east and one in the south west) included a rehabilitation center within the premises, where post-acute rehabilitation was offered to patients. The head physiotherapist in each hospital/ rehabilitation center was contacted in person (by fax or post) in order to identify the number of his/her physiotherapy staff and whether specific guidelines regarding progression and discharge for TKR patients are followed in his/her facility. In cases where specific instructions were followed by all physiotherapists, a single questionnaire was delivered to the facility. If no uniform guidelines were followed, then the head physiotherapist was asked to provide email addresses/contact details from all staff (treating TKR) so as to allow delivery of questionnaires directly to each therapist. Seventy-five physiotherapists from a total of eleven hospitals were contacted in this way as only one hospital had been following uniform guidelines. To minimise non-respondents, an email reminder was sent to the head physiotherapist and the department's staff within three weeks after the initial distribution.

For the outpatient component, as most physiotherapists in Greece work in the private sector in post-acute rehabilitation (Billis *et al*, 2010), private physiotherapists were targeted. Private physiotherapists are either occupied in personally-owned clinics or manage the outpatient department of private rehabilitation centers which they sub-rent. In Greece, it is also legal for academic staff to own private clinics. Thus, from a catalogue of all Greek private registered physiotherapists (n=1,530), accessed from the PPTA registry, a 10 %random sample of physiotherapists was used. Randomisation was performed via Microsoft Excel random number generator. Thus, 150 randomly selected physiotherapists from the private sector were contacted by email. Again, an email reminder was sent to the private physiotherapists within three weeks after the initial distribution.

Participants returned questionnaires by email, post or fax and data was transferred into an SPSS file.

4.2.2 Survey design

The basic format of the selected survey instrument was one that had been used initially in a relevant study in Australia (Naylor *et al*, 2006), and for which permission had been granted for it to be adapted into Greek. For further information, the full questionnaire can be found in the Appendix (Appendix I). The instrument was adapted in Greek by the primary investigator (MM) in the first instance. The translated questionnaire was then edited into its current format following in-depth discussions and the clinical judgment of experienced (>ten years into research and management of knee replacement patients) physiotherapists and orthopedic surgeons, to make it more comprehensible within the Greek culture and healthcare setting. The questionnaire was then piloted in a private rehabilitation center, where 10 physiotherapists (not included in the main sample) completed and commented on the questionnaire before its first distribution. Following minor amendments to the wording expression of a few questions, the final survey questionnaire was comprised of 22 questions from the original questionnaire by Naylor *et al* (2006). It involved questions about the rehabilitation goals, potential factors affecting rehabilitation, outcome measures and protocols used from the inpatient phase of rehabilitation for up to six months post-surgery. Only one question on a therapists' profile (clinical experience, field of work, level of studies) was added (Doody & McAteer, 2002). The current questionnaire consisted of a combination of closed (n = 11) and open-ended questions (n = 12). Open-ended questions were thought to be

necessary, to provide respondents with freedom to expand upon answers given, improving the quality and depth of information gained and to elicit a wider aspect of opinions on issues affecting practice. The inclusion of some open-ended questions was chosen as it has been proved as an effective strategy to increase the response-rate (Nakash *et al*, 2006, Kellerman & Herold, 2001). A survey outline is presented in Table 4.1. It was estimated that the questionnaire required eight to ten minutes to be completed. The survey was distributed from July 2011 to December 2011.

Table 4.1 Content outline of the survey questionnaire.

Therapist's profile	Professional experience, specialty, academic level, Number of TKR treated per year, field of work (inpatient, outpatient) (1 CEQ- 5 subquestions)
Immediate post-operative (inpatient) care (No. of questions)	<ul style="list-style-type: none"> • Length of hospital stay (LOS) (1 CEQ) • Standard physiotherapy practice (1 OEQ) • Discharge criteria (1 OEQ) • Referral after discharge (home with or without supervision, inpatient or outpatient) (1 CEQ)
Outpatient short and long term recovery phase (No. of questions)	<ul style="list-style-type: none"> • Available rehabilitation services (inpatient, outpatient, individual or group, hydrotherapy) (1 OEQ & 1 CEQ) • Assessment tools (for ROM, muscle strength, function etc.) (1 OEQ) • Standard physiotherapy care (3 CEQ & 1 OEQ) • Type of exercise (1 CEQ) • Emphasis of exercise programme (1 OEQ) • Volume of exercise (frequency, duration, intensity, progression criteria) (2 OEQ) • Introduction of balance exercises (timing into physiotherapy programme) (1 OEQ) • Expected functional ability (independency, ADL activities) (2 CEQ) • Primary and secondary goals (focused to address symptoms, function etc.) (2 OEQ) • Residual problems (1 OEQ) • Patient expected goals at discharge-timeline (when and why) (1 CEQ)

ROM: range of motion; ADL: activities of daily living; OEQ: open-ended questions; CEQ: close-ended questions

4.3 Data Analysis

A SPSS data file (SPSS version 16.0, Inc., Chicago, IL, USA) was created by the primary researcher. Descriptive statistics with frequencies and percentages were

used for analysis of closed questions, as most variables were either nominal or ordinal. Further cross-tabulation analysis was used in cases where physiotherapists' responses needed to be further categorised according to a certain criterion (i.e. number of TKR patients seen annually). For the responses to the open-ended questions, the analysis was undertaken by two analysts, the principal investigator and a second analyst, and comprised of the following stages: (1) Transcribing the information. The principal investigator read the responses and created notes on potential themes. (2) Content analysis by principal investigator and second analyst. The principal investigator and the second analyst identified and coded the data into themes and categories independently. This process was followed by the development of interpretations, main issues and concepts from the responses (Krueger, 2000). (3) Discussion between analysts. An in-depth discussion took place when the analysts' versions were revealed. There was agreement on all main categories, and on most themes (Johnson & Waterfield, 2004; Hruschka, 2004). Irrelevant themes were removed (Krueger, 2000), and consensus was finally reached. (4) Development of the English version of the analysed transcripts. The final stage was to translate and develop the English version of all open-ended responses. The principal investigator performed the translation and the second analyst reviewed and verified the translating themes and categories.

4.4 Results

4.4.1 Physiotherapists' profile

Two hundred and twenty-five survey forms were distributed in total (by email and personal contact with the head of the physiotherapy department) and 132 were returned (58.7 % response-rate). The response rate for the inpatient component of the sample reached 63 % (47/75) and the outpatient component reached 57 % (85/150). Of these, 47 (36 %) were completed by physiotherapists, who were seeing patients during the immediate post-operative inpatient phase, and 85 (64 %) by physiotherapists, who were seeing patients after the patients had been discharged. The physiotherapists' profile is presented in Table 4.2.

Furthermore, when cross-tabulation analysis was performed, no noteworthy differences (to make any further comparison with a *t*-test necessary) were found in

the inpatient programme between physiotherapists having reported treating ten, and those having reported treating more than ten TKR patients annually.

Table 4.2 Physiotherapists' Profile (n=132).

Number (percent)		
Area of work	Public Hospital (inpatient)	20 (15.1 %)
	Rehabilitation Centre (inpatient for 27/43 and outpatient 16/43)	43 (32.6 %)
	Private Physiotherapy clinic (outpatient)	34 (25.7 %)
	Home visits	22 (17.0 %)
	Community	10 (7.5 %)
	Other e.g. academic physiotherapists	3(2.0%)
	Clinical experience	1-5 years
	5-10 years	40 (30.3 %)
	Over 10 years	47 (35.6%)
Main area of specialty	Musculoskeletal	31 (23.5 %)
	Neurorehabilitation	19 (14.4 %)
	Orthopaedic	12 (9.1 %)
	Cardiorespiratory	5 (3.8 %)
	Other	9 (6.8 %)
	None	56 (42.4 %)
TKRs treated per year	10	73 (55.2 %)
	10-30	21 (16.2 %)
	30-50	27 (20.0 %)
	>50	11 (8.6 %)

TKR: total knee replacement

4.4.2 Inpatient physiotherapy practice (immediate post-operative)

According to 57.4 % (27/47) of physiotherapists, over half of patients (56.7 %) are discharged with a home exercise programme, usually unsupervised. Inpatient rehabilitation, as unanimously reported, always included gait re-education in conjunction with strengthening and ROM exercises. Table 4.3 presents physiotherapy interventions in the post-operative phases, whilst Table 4.4 presents physiotherapy discharge criteria from hospital. When physiotherapists were further asked to describe some of the standard exercises they used, they unanimously mentioned strengthening and stretching, progressing from lying or sitting positions, on muscles directly acting on the knee, such as the quadriceps, hip and knee flexors.

Table 4.3 Physiotherapy interventions in the post-operative phases.

Setting	Intervention	Percentage of respondents
Inpatient	Transfer training Strengthening (knee extensors, knee & hip flexors) Patella mobilisation Continuous passive motion (CPM) Gait re-education	93.3
	Exercises (stretching & strengthening of knee-related muscle groups); gait re-education (with crutches)	3.3
	Exercises (stretching & strengthening of knee-related muscle groups); stairs	3.3
Discharge from hospital	Closed kinetic strengthening exercises	9.5
	Gait-re-education	1.9
	Functional exercises	5.7
	Closed kinetic strengthening exercises + gait-re-education + functional exercises	21.0
	Closed kinetic strengthening exercises + gait-re-education + functional exercises + balance exercises	50.7
	Closed kinetic strengthening exercises + Gait-re-education + functional exercises + PNF (hold-relax technique) + massage + manual therapy + electrical muscle stimulation	9.5
	Monitored home programme	1.9

PNF: Proprioceptive neuromuscular facilitation.

Table 4.4 Hospital discharge criteria.

Discharge criteria	Outcome measure achieved	Percentage of respondents
ROM	Full extension, 90° flexion	20.0
Gait	Independent gait (40 m)	20.0
	Independent transfers; Compliance with home exercise programme	13.4
Pain	Control of pain	3.3
Stairs	Independent with stairs	10.0
ROM + gait + pain + stairs	All the above	23.3

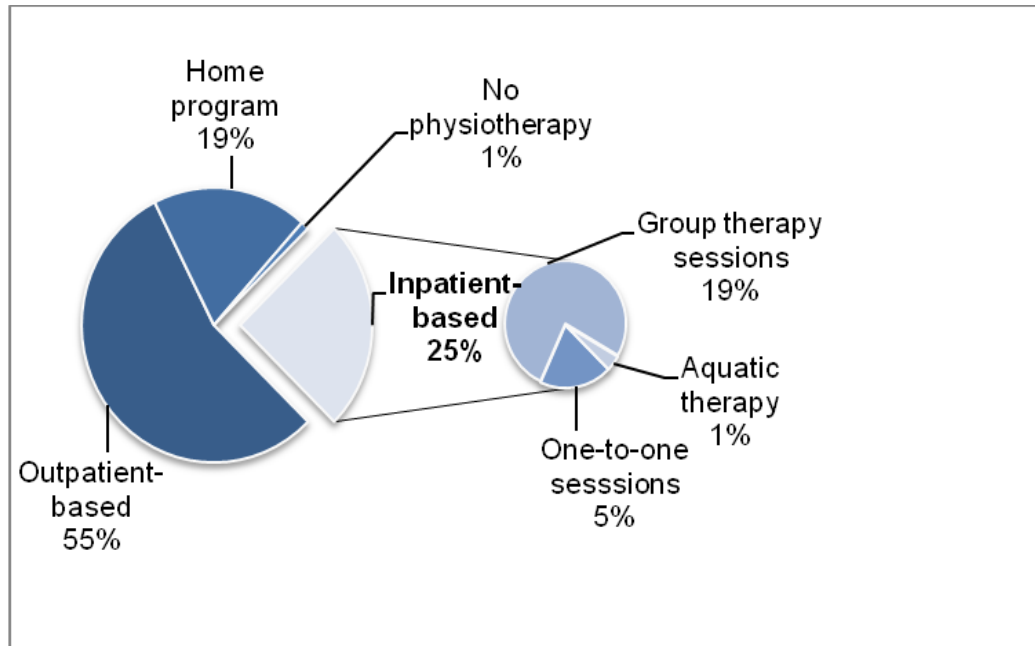
ROM: range of motion.

4.4.3 Physiotherapy practice (short-term rehabilitation period: two weeks to six weeks)

4.4.3.1 Service delivery after hospital discharge

Rehabilitation according to physiotherapists' views offered after discharge either in an inpatient or outpatient basis, is summarised in Table 4.3. Physiotherapy services available for TKR patients after discharge are presented in Figure 4.1. From the physiotherapists who treat patients after hospital discharge ($n = 85$), 31.7 % (27/85), reported that they provide sessions for a period of up to two weeks, 49.2 % (42/85) between two to six weeks, and 19.1 % (16/85) for more than six weeks.

Figure 4.1 Physiotherapy rehabilitation services received after discharge from hospital (according to physiotherapists' views).



4.4.3.2 Rehabilitation goals after hospital discharge

During this course of management, physiotherapists' goals included: a) restoration of muscle strength and ROM (47.2 %, 40/85), b) improved gait (21.1 %, 18/85), c) amelioration of patients' functional status and provision of safe and ergonomic instructions (22.3 %, 19/85), and d) achievement of good balance and proprioception (9.4 %, 8/85).

4.4.3.3 Factors influencing rehabilitation programmes, progression and expected outcome at six weeks

Physiotherapists reported various factors taken under consideration in order to determine and progress the volume and intensity of exercise applied to patients (Table 4.5). Amongst the most commonly reported influential factors for exercise progression were the patient's general health, psychological and behavioral issues, any post-operative complications occurring and surgeons' guidelines. Patients' age, muscle strength and pain levels were also reported but were not the primary determinants.

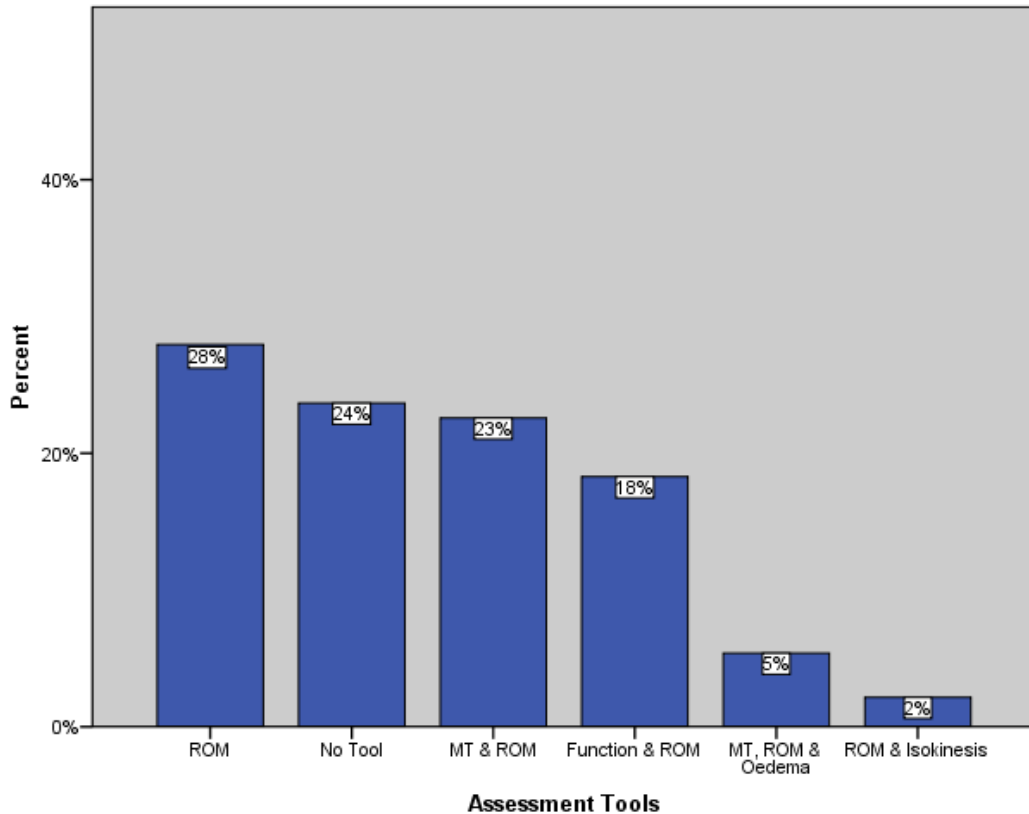
Table 4.5 Factors affecting decision-making in volume of rehabilitation programme.

		Percentage of respondents
Factors affecting selection of primary programme	Patient' complications & social-cognitive attitude towards rehabilitation	61.3
	Patient' general health & current medical status	29.0
	Surgeon' guidelines	3.2
	Patient' health insurance	6.5
Factors affecting volume/ progression of exercise being implemented	Patient' medical status & endurance	75.0
	Patient' effort, psychological status & muscle strength	9.8
	Patient' age & pain levels	9.8
	Patient' post-operative stage & surgeon' guidelines	5.4

4.4.3.4 Outcome measures utilised

Figure 4.2 presents the outcome measures used by physiotherapists to assess patients' progress. As it can be seen from the graph, a significant number of physiotherapists report not using any outcome measure. However, when the frequency of specific outcome measures used (i.e. goniometer, muscle strength testing, and functional measures) was further analysed amongst physiotherapists treating ten or more than ten TKR patients, no noteworthy difference was observed.

Figure 4.2 Assessment tools utilised in everyday clinical practice (n = 132).



ROM: range of motion with goniometer; MT: Manual Muscle testing; Function: functional tests e.g. 6 min walk test, Sit-to-Stand, Timed Up and Go Test; Isokineses: Isokinetic Dynamometer.

4.4.3.5 Final stage of recovery - Functional rehabilitation (six weeks - up to six months)

During this final period, physiotherapists seem to predominantly focus on improving balance and function (64.5 %, 55/85), and to a lesser extent, on balance and endurance (20.5 %, 18/85), or gait asymmetries (6.5 %, 5/85), whilst a small percentage of respondents (8.5 %, 7/85) do not usually treat patients during this period (they seem to stop at four to six weeks). According to physiotherapists' perspectives, there is a range of residual problems determining poor outcome at this stage, including lack of full passive extension (50.6 %, 43/85), quadriceps' muscle weakness (22.6 %, 19/85), inadequate flexion ROM (15.3 %, 13/85), medical history (7 %, 6/85), instability (2.4 %, 2/85), swelling (1 %, 1/85) and patients' fear (1 %, 1/85). Table 4.6 presents the reasons that lead either patients or physiotherapists to end their rehabilitation programme.

Table 4.6 Factors implicated in ending physiotherapy rehabilitation programme.

Criteria for ending physiotherapy (according to patients' views)	Painless & home independence	85 (64.5 %)
	Return to ADL	37 (28.0 %)
	Prescription by orthopedic surgeon	10 (7.5 %)
Factors implicated to ending physiotherapy programme (according to physiotherapists' views)	Patient' complications & motivation	74 (50.9 %)
	Cost covered by Public insurer	8 (6.5 %)
	Complications	7 (5.4 %)
	Surgeon guidelines	4 (3.2 %)
	Medical history	3 (2.2 %)
	All the above (except cost constraints)	20 (6.5 %)
	All the above & cost constraints	16 (11.8 %)

ADL: activities of daily living.

4.5 Discussion

This is the first national survey that describes the current standard practice of TKR rehabilitation according to Greek physiotherapists working in a range of acute, community and outpatient settings. The study is considered pragmatic and the sample is believed to be representative of the physiotherapists' population in Greece because: a) a random sample of all registered Greek physiotherapists with full geographical representation responded to the survey, b) physiotherapists involved in the survey had all been treating at least 10 TKR patients annually, (inpatient or outpatient) c) it purposively reflects physiotherapists' perceptions (both novice and more experienced ones) in hospitals and clinics nationwide, where TKRs are performed, and d) it encompasses rehabilitation centers and private practices, where patients are referred after hospital discharge. The outpatient physiotherapy' sample used was also thought to be representative, as physiotherapists in Greece are mostly employed privately and without having official specialities (Billis *et al*, 2010). The response rate for the inpatient component of the sample reached 63 % (47/75) and the outpatient component reached 57 % (85/150), which are considered acceptable (Instructional Assessment Resources, 2011).

4.5.1 Inpatient physiotherapy practice (immediate post-operative phase)

Rehabilitation strategies are dependent upon the constraints of health-care budgets, patient' income and physiotherapy' protocols (Heck *et al*, 1992; Naylor *et al*, 2009; Pearson *et al*, 2000). Variations in therapists' preferences according to the health system, education and culture had also been expected. Physiotherapists report in

the inpatient phase focusing on ROM, muscle strengthening and gait training. In addition, physiotherapists' duties also encompassed bed mobility and transfers, activities (Dejong *et al*, 2009). An older (1994) British survey from the Association of Orthopedic Chartered Physiotherapists (AOSP) reported the type of exercises utilized which incorporated isometric quadriceps, dynamic quadriceps (0-30°), straight leg raise and active flexion exercises (Frost *et al*, 2002). Continuous passive motion (CPM), cryotherapy and patellar mobilizations are other inpatient interventions reported in the current survey as well as across the literature (Dennis *et al*, 2006; Smith *et al*, 2002) but with inconclusive results for clinical efficacy and effectiveness. Nevertheless, there is evidence to suggest that physiotherapy interventions during the inpatient phase should be more closely linked to ADL (walking, chair rising, stair climbing) than to pure stretching and strengthening exercises used traditionally, in order to prepare patients for the home environment (Frost *et al*, 2002; Grotle *et al*, 2010; Noble *et al*, 2005).

In Greece, there appears to be a variety of available discharge criteria utilised either in combination or separately (i.e. 20 % of therapists reported ROM as the most important achievement, 20 % prioritised short distance gait-capability etc.). The recent trend in the developed countries however, is the utilisation of functional discharge criteria involving transfers, personal care, ability to walk with walker/crutches for >70 m and visual analogue scale (VAS) scores of <5 cm for activity (Husted *et al*, 2011).

4.5.2 Physiotherapy practice after hospital discharge

Following hospital discharge, depending on each country's health-care resources and patient needs, clinical pathways and physiotherapy strategies involve, either outpatient physiotherapy sessions, supervised home-based programmes or no rehabilitation (self-directed) (Barrois *et al*, 2007; Coulter *et al*, 2009; Genet *et al*, 2007; Isaac *et al*, 2007; Kramer *et al*, 2003; Lavernia *et al*, 2006; Moffet *et al*, 2004; Mockford *et al*, 2008; Rajan *et al*, 2004; Shepherd *et al*, 1998). According to Greek physiotherapists, the majority of patients were discharged with a home exercise programme, usually unsupervised, and to a lesser extent discharged to outpatient

physiotherapy. Outpatient physiotherapy is usually offered by a physiotherapist who is contracted with a public health-care insurer (located either in a private physiotherapy facility or at the patient's home). Home programmes were reported by physiotherapists as being more convenient. Interestingly, home programmes (supervised even by regular telephone appointments) are a subject of research as they are preferred by patients and are reported in some studies to be equally effective as outpatient clinic-based rehabilitation (Coulter *et al*, 2009; Galea *et al*, 2008; Genet *et al*, 2007; Mahomed *et al*, 2008; Mitchell *et al*, 2005).

In terms of service availability after discharge, physiotherapists reported that rehabilitation is mostly offered on an outpatient basis (55.2 % compared to 24.8 % for inpatient rehabilitation). Inpatient rehabilitation services in Greece are mostly found in the private sector; however, finances for in-stay rehabilitation are provided partly via public health insurance. In such inpatient facilities, rehabilitation is offered either in group-based programmes or in one-to-one sessions with the availability of aquatic therapy. The concept of group therapy has been introduced in Greece recently. Although one-to-one therapies are identified as more targeted in the literature because patients inherently receive individualized attention, group-based approaches seem to be just as efficient, enjoyable and cost-effective (Aprile *et al*, 2011; Coulter *et al*, 2009). In Australia and in the UK, post-operative rehabilitation is more often conducted within outpatient or community-based services (Lingard *et al*, 2000, Naylor *et al*, 2006). This is in contrast to the USA and Norway, where post-surgical rehabilitation takes place in multidisciplinary inpatient rehabilitation facilities (Dejong *et al*, 2009; Grotle *et al*, 2010). Services involving group therapy are delivered in Australia and England too (Arz *et al*, 2012; Naylor *et al*, 2009). Additionally, the literature has revealed that early home rehabilitation for patients that has been targeted effectively, reduces hospital LOS, thus bringing about savings to the care-provider (Nyland *et al*, 2011).

With post-discharge (up to six weeks) rehabilitation, the vast majority of Greek physiotherapists report a tendency to include functional closed-kinetic chain exercises, gait re-education, and balance exercises focused on function, which is consistent with recent evidence (Codine *et al*, 2004; Klika *et al* 2009; Lavernia *et al*, 2006; Mizner *et al*, 2005; Rossi *et al*, 2010). The use of neuromuscular electrical

stimulation (NMES) was also reported as an additional intervention for stimulating the quadriceps musculature, and has also shown to further enhance strength and function when combined with resistance exercises (Pettersen *et al*, 2009). There was some ambiguity amongst physiotherapists about the inclusion of balance exercises within the first six weeks post-TKR (50.7 % and 21 %, for and against, respectively), despite literature that supports the inclusion of balance exercises in the rehabilitation of TKR patients (Dejong *et al*, 2009; Gage *et al*, 2008; Gauchard *et al*, 2010; Piva *et al*, 2010). Research on the timing of inclusion of exercises in general, and specifically for those addressing balance, is needed as balance exercises, an element recently added even in the early stage of a rehabilitation programme, improves functional ability with no adverse effects i.e. knee effusion (Gauchard *et al*, 2010; Piva *et al*, 2010; Liao *et al*, 2013).

4.5.3 Outcome measures utilised

A significant proportion of physiotherapists (23.7 %) reported not using any outcome measure for assessing patients' progress. Range of motion with muscle testing (22.6 %) and functional outcome measures (i.e. TUG) have been reported (18.3 %) as outcome measures used in the current survey. Therapists would benefit from the use of outcome measures that capture functional assessment in order to monitor and target the functional needs of patients at each stage of a care pathway (Bent *et al*, 2009; Jette *et al*, 2009; Rivard *et al*, 2010; Rolfson *et al*, 2016). Indeed, functional tests such as TUG and outcome scores such as the Western Ontario and McMaster Universities Arthritis Index (WOMAC) are the most frequently used to assess patient's mobility skills in the literature, being valid, reliable, responsive and feasible in clinical practice (Beard *et al*, 2010; Boonstra *et al*, 2008).

4.5.4 Factors influencing rehabilitation programmes, progression and expected outcome at six weeks

Criteria for exercise progression and exercise volume are one of the understudied aspects of rehabilitation. Physiotherapists in the current survey reported that exercise resistance is increased according to patients' capabilities, without utilising objective criteria (i.e. patients' muscle strength was reported by 9.8 % of physiotherapists). Both the findings within this survey and within those from the international literature suggest that physiotherapists do not seem to use specific

milestones or principles for exercise progression (Feller *et al*, 2002; Haas *et al*, 2012). Clinical decision-making process regarding patients' programme progression is based on physiotherapists' clinical experience and reasoning (Edwards *et al*, 2004; Moore, 2004; Blanchard & Glasgow, 2014). Therefore, there appears to be a need for more objective criteria that complement decisions on exercise progression that have previously been gauged using with patient' perceptions of capability. Classification of patient' progress following discharge with categories such as functionally independent, those requiring supervision and those requiring constant assistance, could be a helpful strategy for exercise progression (Olmeadow *et al*, 2002). Preliminary evidence on a high-intensity, long-duration rehabilitation programme, initiated after discharge, indicated significant benefits on muscle strength and functional tasks such as the TUG Test (Bade & Stevens-Lapsley, 2011). Nevertheless, progression in this latter study was again achieved subjectively (dependent upon patients' tolerance or complaints) and not on the achievement of specific milestones.

Although there are studies that highlight the importance of continuing physiotherapy after three months following TKR (Valtonen *et al*, 2009; Woolhead *et al*, 2005), in Greece, most physiotherapists reported usually stopping physiotherapy at this stage. The reasons reported commonly had to do with waivering patient' motivation, and to some extent with patient' financial constraints. This pattern of cessation of care is similar to what has been indicated in the literature (Dexter, 1992). Recovery at six months is reported to be substantially dependent upon pre-operative pain and function (Jones *et al*, 2003).

The current survey of physiotherapists' views highlighted that patients' residual problems are mainly a lack of full passive extension and quadriceps' weakness. At the end of the first post-operative month, patients have been shown to perform ADL with the least dependence for the first time within the initial recovery period after surgery, and contradicted by the most prevalent deficits in muscle strength (up to 60 % compared to the pre-surgery levels) (Mizner *et al*, 2005; Stevens *et al*, 2010). Moreover, the performance in climbing stairs and "stand up and go" returned to pre-operative levels two months post-surgery (Mizner *et al*, 2005). Relevant literature highlights *intensive* rehabilitation programmes with an emphasis on function (Dauty *et al*, 2007; Ouellet & Moffet, 2002) as having the capability to address these deficits. Therefore, maximising functional outcome and quadriceps strength in the

first month after surgery seems to be a challenging area for further research, especially as both factors appear to correlate highly.

4.5.5 Study Limitations

Although every effort was made to provide a fair Greek hospital representation, a relatively small number of hospital-based physiotherapists (15.1 %) participated in the survey. Greek physiotherapists are disproportionately low in hospital-based settings (Billis *et al*, 2010). The analysis of the sample's profile showed that a significant percentage of physiotherapy respondents (55.2 %) treated just over 10 TKR patients annually. This number could be considered relatively low. However, currently no physiotherapy specialty exists in Greece, a physiotherapist's clinical portfolio would most likely show a large variety of patients (Billis *et al*, 2010). Therefore, in order to minimise any possible bias, further cross-tabulation analysis was performed to compare physiotherapists treating ten and those treating greater than thirty TKR patients annually and, interestingly, no noteworthy differences emerged. Additionally, reporting bias cannot be fully excluded as it is considered that not all professionals are willing to answer surveys or to report their views without bias. Self-reported data are often argued to be unreliable and threatened by self-reporting bias (Althubaiti, 2016). Finally, this is a survey study of clinicians based on self-reporting by physiotherapists, and therefore, the data that had been analysed represented indirect measures and not patient-specific data. Consequently, although the results provide clinically useful information, the interpretation should be made with some caution. An additional aim of the study had been to collect information on a therapist's selected dose of treatment, but this could not be determined with suitable precision.

4.6 Conclusion

This is the first Greek national survey to describe physiotherapists' views on the rehabilitation process of patients undergoing TKR. Patients in Greece are described by physiotherapy reports to be mostly discharged with a home-based individualised exercise programme. A consistency in care was described by therapists during inpatient rehabilitation, whilst there seemed to be diversity in the physiotherapy programmes implemented in the short- and long-term outpatient recovery phase.

Strengthening, ROM and functionality seemed to be the primary physiotherapy goals. A significant number of physiotherapists reported not using any specific outcome measure for assessing patients' progress, whereas empirically-based criteria (i.e. patients' medical status, endurance, muscle strength etc.) were used. Most physiotherapists reported that patients tend to stop rehabilitation at approximately three months post-TKR due to waning patient' motivation. Future research should aim at providing guidelines regarding the application and timing of the initiation of optimal dosage, type, and intensity of exercise conditioning. In particular, the optimal implementation of balance-related exercises is a prerequisite for patients' functionality and reflected an area of ambiguity amongst the responses of physiotherapists in this survey.

Chapter 5

**Balance and incidence of falls in patients with knee
osteoarthritis following total knee replacement:
A systematic review.**

Abstract

Background and Purpose: Despite the higher incidence of falls in patients with OA, compared to age-matched controls (Arden *et al*, 2006; Hill *et al*, 2013), few studies have explored whether occurrence of falls is affected after patients undergo TKR. Therefore, the aim of this systematic review was to evaluate the effects of TKR on balance, and number of falls by critically reviewing the available literature.

Methods: A systematic review of published literature sources was conducted up to March 2014. All studies assessing balance and incidence of falls after TKR (without physiotherapeutic intervention) were included. The MEDLINE Mesh keywords used were: Balance OR stability OR postural control OR falls AND knee replacement OR knee arthroplasty in the title or abstract or keywords of the studies. The methodological quality of each study was reviewed using the Critical Appraisal Skill Programme tool.

Results: Fourteen studies were included, comprising of ten cohort studies (Level II), three studies with Level of evidence III and one study with Level of evidence IV.

Conclusions: Findings provide evidence that TKR improves dynamic balance for up to one year following surgery (Level of evidence II-IV). There is an ambiguity as to whether single limbs static balance is improved or remains in the same levels post-TKR. However, both static and dynamic balance remains lower than that of age-matched controls. The incidence of falls remains as high as 40 % - 48 % post-TKR, again higher than that of community elderly people (30 % - 33 %) (Level of evidence II-IV). Knee replacement surgery influences positively fear of falling. It was highlighted that knee extension strength, proprioception and symmetrisation of postural strategies have not fully recovered post-TKR, and influence balance performance. Clinically, these persistent deficits need to be mitigated by physiotherapy even before TKR takes place.

5.1 Introduction

Balance is essential for maintaining postural stability while performing functional activities and for falls' avoidance (Sibley *et al*, 2013). Postural stability can be defined as the ability of an individual to maintain his/her center of gravity (COG) within the base of support. Many complex physiological and neurological systems control balance. The musculoskeletal and CNS are the main systems regulating postural stability, both understood to be acting functionally as one sensori-motor system. Many aspects of the human body, such as the vestibular system, sight, proprioception, muscular strength, and cognition are related to the balance control, which is an important ability in everyday life. Balance (dynamic and static) is a complex function which requires integration of sensory information regarding the position of the body and the ability to make appropriate motor responses to body movement (Hill *et al*, 2013). More precisely, balance depends on sensory input from somato-sensory (proprioception), visual and vestibular systems (Bascuas *et al*, 2013), as well as on the responses of muscles. Static balance refers to maintaining equilibrium while standing in one spot, whereas, dynamic balance involves motion and is defined as maintaining equilibrium during locomotion (Morrow *et al*, 2010). Falls and loss of balance most commonly occur during movement-related tasks such as walking and less frequently, during static activities (Hinnman *et al*, 2002).

Balance deficits have been identified as one of the integral components impairing daily living in patients with knee OA and are associated with an increased risk of falls and poor mobility (Williams *et al*, 2010). Approximately 60 % - 80 % of patients with knee OA report knee instability, which causes activity' limitations (Fitzgerald *et al*, 2004; Schmitt *et al*, 2008). Many researchers have attempted to determine the potential mechanisms causing balance impairments in this population, yet they remain to be fully elucidated (Duffel *et al*, 2014; Khalaj *et al*, 2014; Nguyen *et al*, 2014; Smith *et al*, 2012; Sorensen *et al*, 2014). Age-related impairments to the capacities of physiological systems controlling balance (i.e. vision, proprioception) is one of the potential contributory mechanisms (Ribeiro & Oliveira, 2007; Shipplein *et al*, 1991; Shumway-Cook *et al*, 2000). The presence of knee OA may result in changes that accelerate the deterioration of these systems or compound the effects of ageing. Individuals with knee OA display reductions in quadriceps strength and activation (Hurley *et al*, 1997; Oreilly *et al*, 1998), as well as impairments in knee joint proprioception (Pai *et al*, 1997, Sharma *et al*, 1997). These deficits, in

combination with the ageing process, may culminate in greater impairments to the capability for balance in this patient population (Sharma *et al*, 1997). Knee pain and quadriceps' weakness are associated with increased postural sway (Cammarata *et al*, 2011; Garsden *et al*, 1999; Hassan *et al*, 2002; Koralewitz *et al*, 2000; Lund *et al*, 2008; O'Reilly *et al*, 1998). However, while TKR (treatment of choice for end-stage OA) aims to relieve pain, correct deformities and restore loco-motor function, it is not established whether it has an effect on patients' balance and incidence of falls. Currently 80 % of persons affected by OA already report having some movement limitation, and 20% report not being able to perform major ADLs, with an 11 % of the total affected population reporting the need for personal care (Hinman *et al*, 2002; Ringdahl & Pandit, 2011). Patients with moderate to severe OA exhibited (candidates for TKR) significantly ($p < 0.05$) more balance deficits in all positions than patients with mild OA. The literature suggests that patients with knee OA undergoing TKR, present with a significant loss of balance control and proprioceptive acuity ($p < 0.05$) compared to patients with mild OA and healthy controls (Duffel *et al*, 2014; Khalaj *et al*, 2014; Kul-Panza & Beker, 2006; Lytinen *et al*, 2010; Messier *et al*, 2000; Park *et al*, 2013; Smith *et al*, 2012; Sorensen *et al*, 2014). In a study by Nguyen *et al* (2014) of 2,120 knee OA patients, 18 % reported buckling (sensation of knee giving way during standing), 27 % had sensations of knee instability without buckling, and 9 % reported both symptoms that had been frequently precipitated by fear of falling and poor confidence.

Chronic knee OA pain is reduced after TKR but little is known about the recovery of proprioceptors, neuromuscular control and the joint-related stability of patients after TKR. Conversely, asymmetrical gait patterns and postural sway (in the coronal plane) combined with increased trunk movement forward (in the sagittal plane), observed especially in the early postoperative period, cause balance difficulties and increased risk of falls (Chang *et al*, 2011; Grabiner *et al*, 2008; Hunt *et al*, 2008). McClelland *et al* (2007) found that these patients walk with less knee flexion during the swing phase and an abnormal sagittal movement pattern about the knee (a biphasic moment pattern occurs) compared to controls. It has been suggested that the absence of an ACL is a potential reason. Residual physical deficits as well as proprioception, have been observed up to seven years following TKR, with significant impact on functional status (i.e. postural stability, walking speed, stair ascent/descent) (Benedetti *et al*, 2003; Brander *et al*, 2006; Gauchard *et al*, 2010;

Mizner *et al*, 2005a,b; 2011; Ouellet *et al*, 2002; Pap *et al*, 2000; Valtonen *et al*, 2009; Van der Linden *et al*, 2007; Walsh *et al*, 1998; Yakhadani *et al*, 2010; Yoshida *et al*, 2008). In turn, decreased muscle strength, ROM, and altered movement patterns evident post-surgery, affect the sensory and mechanical function of the joint. Byrne & Prentice (2003) reported that TKR affects the ability of patients to step over an obstacle. Therefore, before implementing any type of exercise training it would be essential to know to what extent and in which time-frame the deficits in functional and balance performance, already defined in OA patients, could be altered by TKR surgery.

Falls are amongst the most common sources of injury and hospitalisation in elderly people (over 65 years old), significantly impairing their quality of life (Todd & Skelton, 2004; Scott, 2005; WHO Global Report on falls prevention, 2007). Osteoarthritis has been shown to be an important risk factor for falls with more than 40 % of all patients, and 64 % of female patients, reporting falls within a year in America (Williams *et al*, 2010; Gillespie *et al*, 2009). The cost of falling is high, both to the individual (physical and psychological trauma) and to the health-care system (financial burden related to surgery and rehabilitation) (Duncan *et al*, 1993; Carroll *et al*, 2005). Patients with severe hip and knee OA, who are awaiting THR or TKR, are reported to have a higher incidence of falls compared to the general population (Mitchell *et al*, 2008). Previous studies have highlighted a particularly high prevalence of falls (>50 %) in samples of elderly (over 65 years old) individuals with osteoarthritis (OA) (Brand *et al*, 2005; Hill *et al*, 2013). The Rotterdam study which involved 2,773 subjects, showed that radiographic knee OA is associated with an increased risk of incident-related vertebral and non-vertebral fractures (Bergink *et al*, 2003). Despite the high incidence of falls in the knee OA clinical population, there is a scarcity of investigations in the literature focusing on the risk of falls and subsequent impairments in function for patients with knee OA after TKR. Furthermore, little is known regarding the role of mechanoreceptors in the control of posture, or about the influence of TKR on postural control, and also, about each aspects' natural recovery.

Thus, there a number of factors that may influence the effect of TKR on balance and risk of falls. The present study used the recommendation of the Prevention of Falls Network Europe group (Lamb *et al*, 2005) where a fall is defined as “an unexpected

event in which participants come to rest on the ground, floor, or lower level". Falls occur as a result of complex interactions among demographic, physical and behavioral risk factors. Throughout the past two decades, risk factors have been identified and categorised as intrinsic or extrinsic factors. Intrinsic factors include demographic and biological factors, while extrinsic factors encompass environmental and behavioral factors (A Global Report on the Epidemiology of falls, accessed 31/10/2018). Based on this rationale, the research question aimed to be answered was: How is the balance status and incidence of falls affected by knee replacement surgery in patients with knee OA? Concurrently, studies including measures that were related to risk of falling such as specific assessment tools, or risk factors related to the incidence of falls, such as fear of falling or variability in the gait pattern were collected and discussed. It is hoped that this review will help in the understanding of the mechanisms associated with the recovery of the systems that control balance post-surgery and identify any balance-related residual problems or falls' risk parameters still intruding after TKR. This may ultimately help in a later stage of this thesis, to support and confirm by scientific evidence, the design of an enhanced rehabilitation programme.

5.2. Materials & Methods

5.2.1 Search Strategy

The electronic databases: the Cochrane Central Register of Controlled Trials (Cochrane Library), MEDLINE, EMBASE (via ProQuest), Biomed Central, Cinahl (via EBSCO host) and Physiotherapy Evidence Database (PEDro) were searched from January 1995 to the present (September 2014). The MEDLINE Mesh keywords used were: Balance OR stability OR postural control OR falls AND knee replacement OR knee arthroplasty in the title or abstract or keywords of the studies. Clinical trials published in the English language were included. The reference lists of all eligible papers were also screened to identify any studies that had been missing from the databases.

5.2.2 Eligibility Criteria

Eligibility assessment was performed independently in a standardised manner (described below), and disagreements amongst reviewers (MM, the primary investigator of the study and RP, physiotherapy academic colleague) were resolved

by consensus. Therefore studies were included if they fulfilled the following four criteria:

- 1) Participants underwent primary TKR.
- 2) No physiotherapeutic intervention/rehabilitation was involved after hospital discharge for TKR.
- 3) Balance, postural control and/or number of falls, falls risk related factors was/were used as outcome measure(s).
- 4) The full paper was published in the English language.

Studies included descriptive (cross sectional or cohort studies), but excluded case studies. All cadaver or animal studies were excluded. Moreover, studies with samples involving patients with RA were excluded.

5.2.3 Study identification

Two evaluators independently selected the studies based on titles and abstracts, and excluded those not related to the subject. The full text was obtained for all papers that were considered potentially relevant. Once collected, these were reviewed by both reviewers to determine if eligibility criteria had been fulfilled. The studies that were finally included were analysed according to a certain structure: author/year, sample, assessment outcome measures, timeline, equipment, study findings and clinically-relevant outcome. The selection criteria were applied to the title, and to the abstract of all articles retrieved in the search of the literature. The full text articles not excluded in the initial selection process were then evaluated for inclusion using the same eligibility criteria.

5.2.4 Critical appraisal

The methodological quality of each study was evaluated according to the Critical Appraisal Skills Programme (CASP) tool (<http://www.casp-uk.net/#!/casp-tools-checklists/c18f8>, Critical Appraisal skills programme for systematic review checklists). This appraisal tool has been widely used in systematic reviews and is recognised to be a valid tool. It is largely designed to familiarise users and readers with study designs and help them evaluate the relevance of the papers to their practice as they contain several subjective elements which may not lend themselves to incorporation in a formal quality assessment. Therefore CASP was selected as a

tool to help clinicians make sense of research evidence and help them to apply evidence in practice. The Critical Appraisal Skills Programme (CASP) tools were developed to teach people how to critically appraise different types of evidence. A systematic review appraisal checklist comprised of 10 questions that aim to help researchers to decide whether a review is valid and reliable. Alongside each question there are hints that help you understand what is intended by the question and what to look for in order to answer it. The tool evaluates domains such as: study design, appropriateness of design, randomisation method, blinding, accuracy in the description of the sample's recruitment, treatment' effects, findings' interpretation.

5.2.5 Data Analysis

In the first stage, a descriptive review of studies assessing balance and falls' incidence and/or falls' risk related outcomes in patients after knee replacement was undertaken (Table 5.1).

In the next stage, the analysis involved a critical appraisal process of the studies according to the CASP tool to determine the methodological quality and to summarise findings (Table 5.2). The CASP is comprised of 10 questions in order to screen the included studies and to judge the trustworthiness of research evidence. More specifically, aspects of acceptable cohort recruitment (cohort representativeness of a defined population, existence of any selection bias), accurate measurement of outcomes (reliability, validity of outcome measures), and precision of results (presentation of confidence intervals) etc.

Evidence' level was indicated by RCTs, cohort studies and case-control studies using the following labels (<http://www.elsevier.com/data/promismisc/LevelsofEvidence.pdf>):

Level I: RCTs.

Level IIa: Good studies, with a non-randomised control group (cohort or case/control) correcting for confounding in the analysis.

Level IIb: Poor studies with non-randomised control group, data gathered at the event, poorly matched groups, no attempt to correct for confounding.

Level III: Observational studies Case control studies

Level IV: Case series (poor quality cohort and case control).

All data extracted from the studies were analysed independently by each reviewer and subsequently discussed. In any case of disagreement, further discussion was performed with a third reviewer (NG), to reach a mutual agreement.

An independent statistician (RR) of the QM University was consulted to examine the possibility of a potential meta-analysis by collating data from the included studies. Two options of potential meta-analysis were investigated: The first option collated data from three studies (Schwartz *et al*, 2012; Quagliarella *et al*, 2011; Viton *et al*, 2002) regarding the research question of how dynamic balance (via movement velocity) is affected by TKR. The second option collated data from two studies (Schwartz *et al*, 2012; Swinkels *et al*, 2013) investigating the research question involving how TKR influences functional mobility and risk of falls (via TUG). However, due to the low to moderate methodological quality of studies, the diversity of research designs (using either the pre-surgery condition or age-matched controls as a comparator), the diversity in presenting the descriptive statistics (i.e. TUG presented as mean or median values), as well as the variety of outcome measures related to static and dynamic balance performance, it was concluded that the pooled data would not offer sufficiently informative evidence.

Performance-based measures of static or dynamic balance were assessed in patients after TKR. Regarding falls-related measures, information on the occurrence of falls post-operatively either by a comparison to the pre-operative state of patients or by comparison to aged matched controls was taken. Falls' risk-related measures such as fear of falling or physiological-related factors such as gait variability were also thought to add useful information in the study, as the parameters related to falls and the strategy adopted by patients following TKR would help the understanding mechanism/cause underpinning falls.

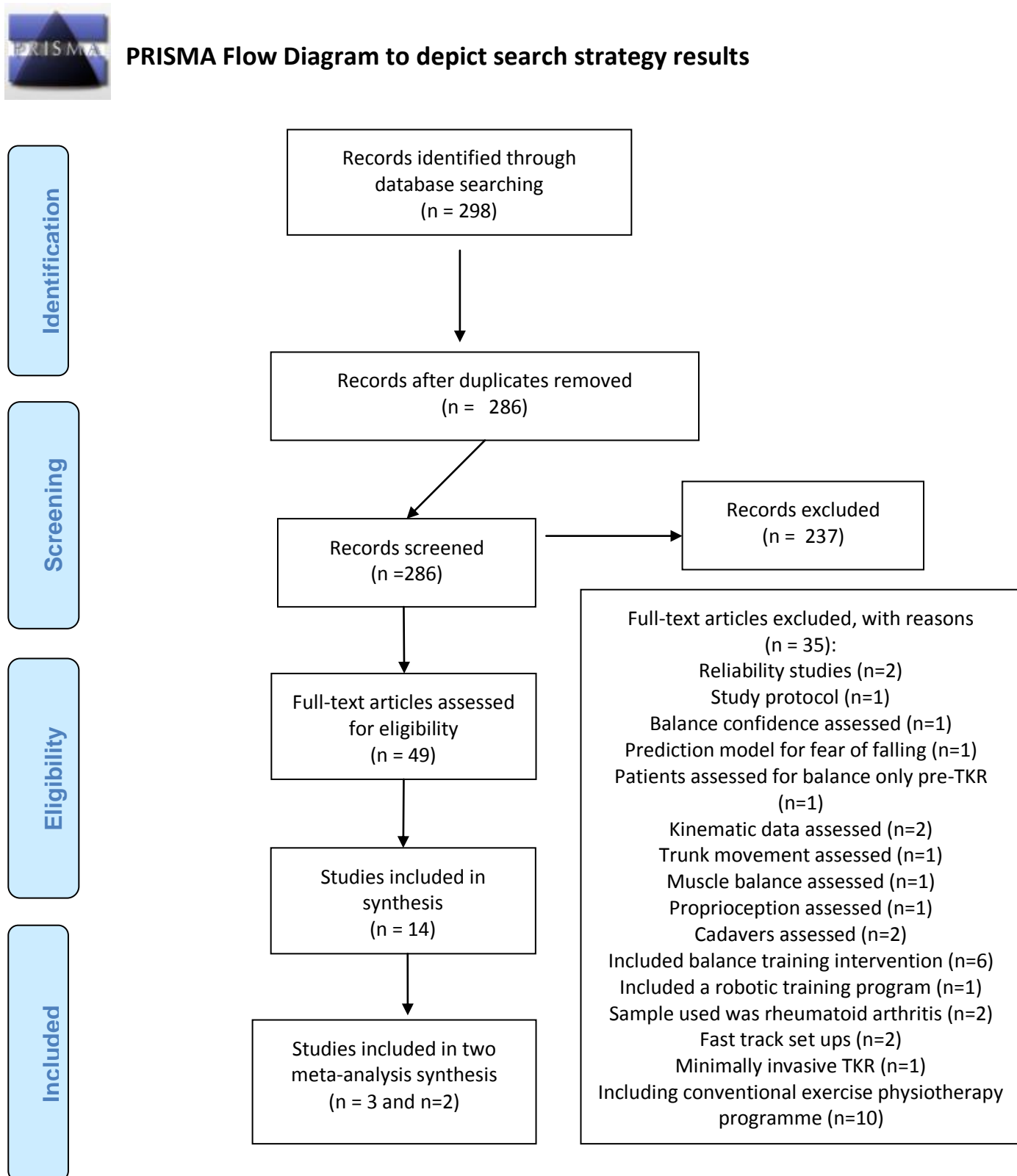
5.3 Results

5.3.1 Search results

A total of 298 citations were identified by the search strategy, summarised in Figure 5.1. Initially, 237 studies were eliminated because the title, abstract or keywords did not match the proposed theme. Of the 61 that remained, 47 were eliminated due to the non-English language used or due to the other aforementioned exclusion

criteria. Therefore, 14 studies were deemed eligible and were finally included in the review.

Figure 5.1 PRISMA Flow Diagram depicting the search strategy of the systematic review.



5.3.2 Cohort characteristics

In all studies, patients had primary OA (grade III-IV according to the Kellgren and Lawrence system (Kellgren & Lawrence, 1957) and fulfilled criteria to undergo TKR. All knees were implanted with the same type of cemented prosthesis (unilaterally or bilaterally). No patellar component was inserted in patients within any of the studies. The control group consisted of healthy age-matched controls.

A description of the included studies, with the outcome measures used, the follow-up period and the clinically-relevant findings is presented in Table 5.2.

Table 5.2 Description of the included studies in the systematic review investigating balance and risk of falls in TKR patients.

	SAMPLE	OUTCOME MEASURES	TIMELINE	CLINICALLY RELEVANT FINDINGS TO BALANCE AND FALLS	STUDY FINDINGS
Cho & Hwang, 2012	n = 11(11F); No CG. Age: 61.7 ± 7.3 years. Inclusion: Radiographic varus deformity & medial compartment OA degeneration undergoing TKR	VAS; WOMAC; varus angle; SLSB in horizontal plane force platform; peak torque of quadriceps	Pre-TKR & 11 days post-TKR	Improvement (~60 %) in SLSB post-TKR	•Stat. sig improvement in SLSB Mean (SD) 30.3 ± 20.8 cm to 18.5 ± 9.3 cm ($p < 0.05$) 11 days post-TKR.
Gage <i>et al</i> , 2007	EG: n = 8(2M,6F) Age: 62.9 ± 6.0 years; CG: n = 9 (5M,4F) Age: 62.1 ± 5.6 years. Inclusion: post-TKR patients, first right TKR, at least 6 months after surgery	EMG and kinematic responses with rotational sagittal plane perturbation platform	At least 6 months post-TKR	No difference between groups in dynamic balance in sagittal plane	<ul style="list-style-type: none"> •Dynamic balance not impaired in EG vs. CG in sagittal plane •Whole body COM displacement not different between groups vs. knee joint angle displacement and EMG => different strategy to maintain balance from CG •TKR modifies the magnitude but not the temporal organisation of muscle response following sagittal plane support surface rotation. •EMG and kinematic responses in EG are bilateral despite unilateral joint disease.

Gage <i>et al</i> , 2008	EG: n = 8(6F) Age: 62.9±6.0 years; CG: n = 9(4F) Age: 62.1 ± 5.6 years. Inclusion: post-TKR patients, first right TKR, at least 6 months after surgery	EMG and kinematic responses with rotational frontal plane perturbation platform	At least 6 months post-TKR	Impaired dynamic balance OF EG vs. CG in frontal plane	<ul style="list-style-type: none"> •Dynamic balance control impaired in EG vs. CG in frontal plane • increased (26 %) COM displacement in EG vs. CG • Differences in joint angle displacement and EMG of EG vs. CG => different strategy to maintain balance from CG •EMG and kinematic responses among patients are bilateral despite unilateral joint disease
Levinger <i>et al</i> , 2011	EG: n = 35 (16F) Age: 67.4 ± 7.0 years; CG: n = 27 (14F) Age: 65 ± 11.0 years. Inclusion: patients with knee OA who could walk independently for 45 m undergoing TKR.	QoL; WOMAC; IPAQ;FES-I;PPA for falls risk	Pre-TKR & 4 months post-TKR	<p>Increased risk of falls in EG compared to CG.</p> <p>Improved SLSB of EG post-TKR but impaired vs. CG.</p>	<ul style="list-style-type: none"> •Higher incidence of falls for EG vs CG 12 months prior surgery: Mean (SD) (48 % (17) vs 30 % (8), respectively). •Fear of falling reduced post-TKR but remained high. Mean (SD): EG pre-surgery 11.4 (3.0) to 9.7 (2.9) post-surgery vs 7.6 (1.2) for CG ($p < 0.05$). • Stat. sig difference in reaction time for EG: 231.3 (31.7) ms pre-surgery to 208.8 (32.2) ms post-surgery. •No significant difference in postural sway (EO) between groups

Levinger <i>et al</i> , 2012	EG: n = 35 (16F) Age: 67.4 ± 7.0 years Inclusion: patients with knee OA who could walk independently for 45 m undergoing TKR.	QoL; WOMAC; IPAQ; FES-I; PPA for falls risk; number of falls	Pre-TKR & 12 months post-TKR	Balance and number of falls remained similar pre-TKR and 12 months post-TKR.	<ul style="list-style-type: none"> •Stat sig. less muscle strength and poorer proprioception for the EG post-TKR compared with the CG ($p < 0.05$).
Mandeville <i>et al</i> , 2008	EG: n = 19(14F) Age: 64.0 ± 7.7 years; CG: n = 21(13F) Age: 63.1 ± 4.3 years Inclusion: end-stage OA undergoing TKR	VAS;WOMAC; obstacle overcoming; kinematic displacement on force platform during gait	Within 2 weeks pre-TKR and 6 months post-TKR	Impaired dynamic balance in EG vs. controls	<ul style="list-style-type: none"> •No sig differences between number of falls pre- and 12-months post (48.5 (17) % pre- vs 40 % (14) post-surgery reporting at least one fall) •No sig difference in postural sway •Sig improvements ($p < 0.001$) in extension strength, fear of falling (11.4 (3.0) pre-TKR vs 9.4 (2.3) post-TKR) and reaction time (231.3 (31.7) pre-TKR vs 209.1 (31.3) post-TKR. •Improvement in WOMAC post-surgery •Poorer gait stability in EG (smaller displacement COM/COP) than CG •Stat sig. smaller ($p < 0.001$) CO/COP displacement (m) for EG (0.080 (0.048) pre-TKR to 0.075 (0.035) post-TKR vs CG (0.082 (0.043) to 0.071 (0.032) during crossing obstacles.
Mauer <i>et al</i> , 2005	EG: n = 29(19F) Age: 72.6 ± 5.4 years; bilateral (BL) TKR. CG: n = 27(17F) Age: 70.6 ± 5.5. Inclusion: knee OA who	Balance (SLSB for 30 s); Obstacle avoidance success rate	EG tested post-TKR: 2.75 ± 1.29 (range: 1-5	Impaired SLSB in EG vs. CG. Increased risk of falls in EG vs.	<ul style="list-style-type: none"> •Stat sig less SLSB (s) for EG: 6.8 (7.5) vs CG: 18.7 (8.8), $p < 0.001$. • Stat sig less obstacle

McChesney & Woolacot, 2000	could climb stairs, rise from a chair, have 20/40 vision or better undergoing TKR n = 22 Age: ≥ 70 years; Groups: knee OA, ankle OA, patients undergoing TKR	TJPS; EMG and kinematic responses with force platform	years) Not stated	CG No difference on static or dynamic balance of TKR patients compared to controls.	avoidance success rate for EG: 0.044 (0.27) vs CG: 0.65 (0.25), p<0.005. •TKR patients showed no stat. sig difference of COP in any direction, with EO or EC. •TKR had no effect on the automatics postural response muscle onset latency. • TJPS of the knee and/or ankle was not affected by TKR (ns).
Quagliarella <i>et al</i> , 2011	n = 240(142F) EG1: n = 81 THR Age range: 40-80 / 42-82 years; EG2: n = 100 TKR Age range: 48 – 80 / 48-79 years CG: n = 59 Age 67.4 ± 5.9 years. Patients able to stand without support for 120 s.	Posturography on force plate	Pre-TKR; 6 months &12 months post-TKR	Standing balance did not show a clear trend towards improvement in patients following TKR.	•No statistically significant improvement in posturographic parameters of patients following TKR at follow-ups. •Statistically significant improvement on pain and function post-TKR. •Posturography not recommended as a method to evaluate balance in TKR patients.
Schwartz <i>et al</i> , 2012	n = 62(52F) mAge: 73 (r: 57-83) years. Inclusion: Knee OA patients able to walk & follow simple instructions undergoing TKR	Dynamic & static Balance with force platform on foam and firm surfaces with EO, EC; TUG; SF-36	Pre-TKR & 12-months post-TKR	Significant improvement in dynamic and functional balance; Significant	•Stat sig. improvement (p<0.001) in functional balance FSST: pre-surgery: 26.2 (17.3) to16.5 (12.1) post-TKR • Stat. sig. improvement (p<0.05) in dynamic balance

				improvement in selected cases of static balance.	RT: pre-surgery: 1.28 (0.48) to 1.4 (0.43). •Stat sig. improvement ($p<0.05$) in static balance measures only on foam surface with EO: pre-surgery: 0.89 (0.31) to 0.91 (0.81).
Swinkels <i>et al</i> , 2009	n = 99(63F) Age 73.4±4.9 Inclusion: primary TKR	falls number; WOMAC; ABC-UK; GDS	Pre-TKR and 12 months post-TKR	Significant switch of pre-TKR fallers becoming non-fallers post-TKR	<ul style="list-style-type: none"> •~54 % (13/24) of pre-operative fallers did not fall again in the first year post-TKR. •~45 % (11/24) patients remained fallers in the first year post-TKR • Stat sig. improvement ($p<0.05$) in balance confidence, WOMAC and GDS post-TKR
Swinkels & Allain, 2013	n = 22 (16F/ Age: 74.8 ± 5.2 years) Inclusion: primary TKR.	falls number; WOMAC, ABC, GDS; BBS; TUG	2-50 days pre-TKR (Mean:23) 143-218 days post-TKR (Mean:183)	Functional balance improved post-TKR in 54 % of patients.	<ul style="list-style-type: none"> •No stat. sig improvement in functional balance (BBS) post-TKR; 41 % of patients exceeded MDC₉₅ for BBS post-surgery •Stat. sig improvement ($p<0.01$) in TUG post-TKR; 50 % of patients exceeded MDC₉₀ for TUG post-surgery • Findings on fallers are

Viton <i>et al</i> , 2002	20 patients EG: n = 8(3F) Age: 67 (46-77); CG: n = 12(6F) Inclusion: Unilateral TKR	VAS; kinetics/kinematics in side step on force platform	15 days pre- and 12 months post- TKR	SLSB improved on operated limb during tasks. Despite improvements in posturomotor strategies after TKR, impairments persisted compared to CG.	restricted by the small sample size. • No stat. sig. improvement in SLSB or double limb standing balance (ms) of the operated limb or non-op. post-TKR
Yakhdani <i>et al</i> , 2011	EG: n = 14(10F) Age 61.6 ± 10 years. CG: n = 12(7F) Age 62.0 ± 12.6. Inclusion: Unilateral knee OA undergoing TKR, sufficient physical condition	Dynamic balance; falls number; gait kinematics	pre-TKR, at 6 weeks, at 6 and 12 months post- TKR	Reduced number of falls and improved dynamic stability post- operatively	• Stat. sig. increase of stability post-TKR ($p < 0.005$). Decreased gait variability and reduced number of falls (1- year pre-surgery: 21 to 141- year post-TKR).

TKR: total knee replacement; EG: experimental group; CG: control group; OA: osteoarthritis; VAS: Visual Analogue Scale; BBS: Berg Balance Scale; TUG: Timed Up and Go; SLSB: Single Limb Standing Balance, ABC-UK: Activities-specific Balance Confidence (ABC) Scale-UK; GDS: Geriatric Depression Scale; IPAQ: Incidental and Planned Activity Questionnaire; FES-I: Falls Efficacy Scale; PPA: FSST: Four square step test; EO: eyes open, EC: eyes closed; Physiological Profile Assessment for falls risk; TJPS: threshold joint position sense; SF1-2: Short-Form 12; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

5.3.3 Outcome measures

In terms of outcome measures and equipment, a list of different methods and evaluation protocols were used in order to investigate balance, incidence and risk of falls. In the absence of a 'gold standard' method to assess balance, content validity of the methods has been investigated (Sibley *et al*, 2014). All studies used validated measures to assess performance-based parameters of balance. Parameters used were static or dynamic balance during either single or double leg stance, or during a functional task e.g. forward reach test, sit-to-stand or overcoming an obstacle. Functional stability limits, reactive control, control of balance during an active task and standing balance are all balance' components being investigated in the studies, all linked with balance-related falls (Levinger *et al*, 2011). More sophisticated equipment such as force plate- and balance-platform-derived measuring parameters, including postural sway, transfer in the center of mass (COM) or center of pressure (COP), and clinical test sensory interaction on balance (mCSIB), were used in seven studies (Table 5.2).

Regarding the incidence of falls after TKR, five studies included number of falls assessment (Levinger *et al*, 2011; Levinger *et al*, 2012; Swinkels *et al*, 2009; Swinkels & Allain, 2013; Yakhdani *et al*, 2010) and three studies reported risk of falls assessment in addition to balance assessment (Levinger *et al*, 2011; Levinger *et al*, 2012; Yakhdani *et al*, 2010). Four studies used a falls-recording diary. One study used the short-form of the Physical Profile Assessment (PPA) that encompasses five tests (proprioception, knee strength, postural sway in two directions and reaction time) to assess risk of falls (Levinger *et al*, 2011; Levinger *et al*, 2011 2012). The PPA is a validated and reliable tool and has been demonstrated to have a predictive accuracy of 75 % for prospectively documented falls in older people (Lord *et al*, 2003). The PPA uses a discriminant function to compute a standardised falls risk score. The level of falls risk according to the overall falls risk score is classified as follows: <0-low risk, 0-1 mild risk, 1-2 moderate risk and >2 high risk. Two studies recorded falls with monthly diaries for 12 months post-operatively (Yakhdani *et al*, 2010; Levinger *et al*, 2012) and four studies followed up patients four to six months after TKR.

5.3.4 Follow-up

Ten studies followed-up patients for up to one year after TKR and compared pre-operative status with post-operative capability, whereas three studies followed-up patients for four to six months only (Levinger *et al*, 2011; Mandeville *et al*, 2008; Venema *et al*, 2012). In four studies, patients were evaluated at least six months after surgery and compared with healthy age-matched controls without any follow-up (Gage *et al*, 2007; 2008; Mauer *et al*, 2005; McChesney & Woolacot, 2000).

The quality of the studies has been assessed in the next stage, as although all studies satisfied a similar number of criteria, their methodologies varied substantially.

5.3.5 Critical appraisal of studies' methodological quality

The results of the critical appraisal are presented in Table 5.3. All studies offered clearly defined research questions, population' characteristics and methods of assessing balance.

Of the fourteen studies included in the systematic review, ten followed a cohort design (Level IIc), seven of which included a control group (McChesney & Woolacot, 2000; Cho & Hwang, 2012; Levinger *et al*, 2011; Mandeville *et al*, 2008; Quagliarella *et al*, 2011; Viton *et al*, 2002; Yahkdani *et al*, 2010). Three studies were observation case-control studies (Level III) (Gage *et al*, 2007; Gage *et al*, 2008; Swinkels *et al*, 2009) and one study was observation study (Level IV) (Levinger *et al*, 2012). The quality of the studies has been assessed as although all studies satisfied a similar number of criteria, their methodologies varied substantially.

Each of this review's studies provided a clear description of the sample in terms of numbers, age, gender and pathology. In 5 studies (Cho & Hwang, 2012; Schwartz *et al*, 2012; Swinkels *et al*; 2009; Swinkels & Allain, 2013; Yakhdani *et al*, 2010), a number of participants (2-15) were lost to follow-ups, implying potential bias. Only three studies had based their sample on a power calculation analysis (Cho & Hwang, 2012; Swinkels *et al*; 2009; Swinkels & Allain, 2013). In relation to interpretation, all studies discussed their findings based on current evidence. Generalisation of findings was feasible in only two studies (Cho & Hwang, 2012;

Swinkels *et al*, 2009), as in the other ones, either the sample size was not sufficient, or the control group was absent.

Table 5.3 Assessment of the quality of the studies included in the current systematic review with the CASP Checklist.

	Cho et al, 2012	Gage et al, 2007	Gage et al, 2008	Levinger et al, 2011	Levinger et al, 2012	Mandeville et al, 2008	Mauer et al, 2005	McChesney & Woolacot, 2000	Quagliarella et al, 2011	Schwartz et al, 2012
Clearly focused issue	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Acceptable patient recruitment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Randomized patient assignment	NA	NA	NA	NA	NA	✓	NA	X	✓	NA
Sample based on power calculation	✓	X	X	X	✓	X	X	X	X	X
Patients fulfilled follow-ups	X	✓	✓	✓	✓	✓	NA	✓	✓	X
Patients, examiners blinded	✓	X	X	X	X	✓	NS	NS	X	NA
Similarity of patients/groups	✓	✓	✓	✓	✓	✓	✓	✓	X	NA
Equal treatment of patients/groups	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clearly specified outcome measures	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Large treatment effect	✓	✓	✓	✓	X	✓	✓	✓	X	✓
Estimate treatment effect (CI)	✓	NS	NS	✓	X	X	✓	X	✓	X
Appropriate results analysis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Confounding factors listed	✓	X	X	✓	✓	✓	✓	X	X	✓
Appropriate interpretation of results	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Generalization of results	✓	X	X	X	X	X	X	X	X	X
Applicable to clinical practice	✓	✓	X	✓	✓	✓	✓	✓	✓	X
Results coincide with relevant literature	✓	✓	✓	✓	✓	✓	✓	✓	X	X
Our evaluation	Reasonable Short-term follow-up	Reasonable Potential bias due to small sample size	Reasonable Potential bias due to small sample size.	Good	Good	Good	Good	Reasonable CI not reported	Outcome measures used not recommended for TKR population	Reasonable ,potential bias due to large numbers lost to follow up

CI: Confidence Intervals; NA: not applicable; NS: not stated.

Table 5.3 CASP Checklist for the studies included in the current systematic review (continued)

	Swinkels et al, 2009	Swinkels et al, 2012	Viton et al, 2002	Yakdhani et al, 2010
Clearly focused issue	✓	✓	✓	✓
Acceptable patient recruitment	✓	✓	✓	✓
Randomized patient assignment	✓	✓	NA	NA
Sample based on power calculation	✓	✓	X	X
Patients fulfilled follow-ups	✓	X	✓	X
Patients, examiners blinded	X	✓	NS	NS
Similarity of patients/groups	✓	✓	✓	✓
Equal treatment of patients/groups	✓	✓	✓	✓
Clearly specified outcome measures	✓	✓	✓	✓
Large treatment effect	X	X	X	✓
Estimate treatment effect (CI)	X	NS	NS	NS
Appropriate results analysis	✓	✓	✓	✓
Confounding factors listed	✓	✓	X	✓
Appropriate interpretation of results	✓	✓	✓	✓
Generalization of results	X	X	X	X
Applicable to clinical practice	✓	✓	X	✓
Results coincide with relevant literature	✓	✓	X	✓
Our evaluation	Reasonable, considerable losses to follow up	Reasonable. Potential bias due to small sample size	Reasonable Potential bias due to small sample size	Reasonable . Potential bias due to small sample size

CI: Confidence Intervals; NA: not applicable; NS: not stated.

5.3.6 Synthesis of Results

5.3.6.1 Static balance post-TKR

Three studies showed statistically significant improvement in static single limb stance (SLSB) and reaction time compared to pre-surgery ($p < 0.001$) 10 % - 60 % (Cho & Hwang, 2012; Levinger *et al*, 2011; Levinger *et al*, 2012) and one study, a trend towards improvement (Viton *et al*, 2002). More specifically, postural sway in SLSB was improved ~60 % at 11 days after TKR compared to pre-surgery (Cho & Hwang, 2012). However, two studies reported no significant difference in SLSB compared to pre-surgery (Quagliarella *et al*, 2011; Schwartz *et al*, 2012). In double limb stance, no difference in postural sway was noted up to one year post-TKR (Levinger *et al*, 2011; Levinger *et al*, 2012).

Patients with TKR presented with 67 % less ($p < 0.05$) mean single leg stance duration than that of healthy controls (Mauer *et al*, 2005). When balance was perturbed in a sagittal plane, no difference in balance control was observed between TKR patients and age-matched controls (Gage *et al*, 2007). However, when balance was perturbed in the frontal plane, control of balance showed statistically significant impairment (larger whole body center of mass (COM) movements, trunk and pelvic rotations) in TKR patients compared to controls, (Gage *et al*, 2008). Interestingly, patients tended to actively resist knee joint flexion (potentially due to biomechanical stiffness of the operated knee) by increasing the activity of rectus femoris and decreasing the activity of tibialis anterior and gastrocnemius.

5.3.6.2 Dynamic balance post-TKR

Three studies showed improved dynamic and functional balance post-TKR compared to pre-surgery up to 37 % (Schwartz *et al*, 2012; Yahkdani *et al*, 2011; Swinkels *et al*, 2013). During tasks such as stepping down, lateral steps, obstacle crossing, the success rate was increased after TKR. However, statistically significant conservative strategies (slower speed, shorter stride length, shorter base of support) ($p < 0.05$) were adopted resulting in increased duration of each task of up to 30 % (Cho & Hwang, 2012; Mandeville *et al*, 2008; Mauer *et al*, 2005; Schwartz *et al*, 2012; Viton *et al*, 2002).

In the sagittal plane, two studies support no difference in TKR patients' postural sway during dynamic tasks (Gage *et al*, 2007; McChesney & Woolacot, 2000) and one study supports impaired balance compared to age-matched controls (Mandeville *et al*, 2008). Nevertheless, in the frontal plane, two studies showed impaired dynamic balance compared to age-matched controls (Gage *et al*, 2008; McChesney & Woolacot, 2000). During a dynamic task, patients with bilateral TKR present with a mean obstacle avoidance success rate that was 32 % less than that of the control group (Mauer *et al*, 2005).

5.3.6.3 Incidence of falls and falls' risk

There is an ambiguity between studies as to how number of falls is affected after TKR. Swinkels *et al* (2009) have reported less than half (45.8 %) of pre-operative fallers continued to fall after TKR. On the other hand, Levinger *et al*, (2012) reported no significant difference (ns) in the number of falls one year post-operatively, with 48 % of patients reporting a fall pre-operatively and 40 % post-operatively. Patients who fell pre-operatively had an 8-fold increase in the risk of post-operative falling (Swinkels *et al*, 2009). A lower falls' risk was reported in four studies after surgery (Levinger *et al*, 2011; Swinkels *et al*, 2009; Swinkels & Allain, 2013, Yakhdani *et al*, 2010). In the PPA risk of falls assessment tool, The overall PPA score did not differ significantly between pre- and post-surgery; however, significant improvements were found for the knee extension strength and reaction time while balance and lower limb proprioception remained similar to the pre-surgery values (Levinger *et al*, 2011; 2012). Balance confidence (ABC-UK) was significantly improved after TKR; however, results remained statistically significant ($p < 0.001$) only in patients with no history of falls pre-operatively (Swinkels & Allain, 2013). Patients with higher ABC-UK pre-operatively reduced the odds of becoming a faller for up to one year post-operatively by 98 % (95 % CI 0.96-1.01; $p = 0.04$) (Swinkels & Allain, 2013). Berg Balance Scale scores of fallers and non-fallers were similar both before and after TKR, although scores were improved, more than the minimal detectable change (MDC) in 41 % of TKR patients (Swinkels *et al*, 2009). Reduced gait variability was positively related to reduced number of falls (Yakhdani *et al*, 2011).

5.4 Discussion

The most important finding of the present study was that TKR seems to positively influence dynamic balance for up to one year following surgery compared to the pre-

operative condition (up to 37 %). However, this improvement was not unanimously reported for single limb static balance, where a dichotomy appeared amongst studies that either showed no difference (two studies) or an improvement post-TKR (four studies) (10 % - 60 %). Regarding falls-related measures again an ambiguity appeared between studies whether incidence of falls actually differs post-TKR. However, all studies showed higher incidence of falls 40 % – 49 % compared to community elderly people (30 %). Fear of falling was positively influenced post-TKR. The rationale for the study was that by analysing the available literature on balanced and falls-related measures, an understanding might be promoted of how mechanisms controlling balance, compensate or respond after surgery, and in which time-line this occurs. This synthesis of information would ultimately help to evaluate the extent and type of remaining deficits after TKR, in order to design a relevant exercise programme targeted to patient' specific needs. Because of the heterogeneity in methodological aspects of the studies included, results from a potential meta-analysis (with an $I^2 > 85\%$) could not have been added because there had been a lack of consistency of evidence.

At the moment, there is only preliminary evidence to underpin the use of balance elements within a physiotherapy rehabilitation programme (Piva *et al*, 2010; Liao *et al*, 2013). Parameters such as the timing, duration, volume and frequency of this exercise regime are still an area under investigation. However, since patients' balance-confidence improved only in pre-operative non-fallers and not in fallers, falls' prevention programmes should commence during the pre-operative period to address deficiencies in this group. Moreover, knee strength and proprioception showed statistically significant improvement after TKR, whereas postural sway with eyes open and reaction time did not (Levinger *et al*, 2011). Therefore, physiotherapy programmes should incorporate the factors that had responded significantly (knee strength and proprioception) and encourage patients who exercise to improve balance and to do so also with eyes closed.

Fourteen studies fulfilled criteria that had been set and were ultimately used in the review. No study involving the use of a post-hospital discharge physiotherapy intervention or, any other type of rehabilitation training, which might otherwise confound the extent of the isolated influence of surgery, was included in this review. Despite a large number of studies in this field, very few offered a high-level of

evidence (Level of evidence < IIb). The sample in the studies comprised of 677 individuals in total (167 being controls), with a mean age of 69.4 years (range 46-84); recruited patient characteristics were typical of elderly individuals undergoing TKR for knee OA, and was therefore considered to be representative of the TKR population. The methodological quality of the studies, as assessed by the CASP scale, was acceptable. However, due to variability in sampling procedure and the absence of power calculation analysis in most studies, external validity and therefore generalisability, has been limited. Major drawbacks in the studies were the lack of randomisation and the lack of a control group in some studies.

Regarding the balance effects found in most studies, there was a significant balance improvement ($p < 0.001$) both in tasks and confidence after TKR compared to the pre-operative state. While balance and sensori-motor performance was not fully restored after TKR, postural responses began to normalise both in quiet stance and dynamic tasks (Mandeville *et al*, 2008; Mauer *et al*, 2005; Viton *et al*, 2002). Static balance did not show a clear trend towards improvement (Qualiarella *et al*, 2011). Single leg standing balance improved up to 60 % post-TKR, but remained poorer than age-matched controls for up to one year (Cho & Hwang, 2012, Levinger *et al*, 2011, Mauer *et al*, 2005; Schwartz *et al*, 2012; Viton *et al*, 2008). Dynamic and functional balance was found to be improved six months post-surgery but again, had not fully recovered compared to age-matched controls (Mandeville *et al*, 2008; Schwartz *et al*, 2012; Swinkels *et al*; 2009; Swinkels & Allain, 2013; Yakhdani *et al*, 2010).

In studies investigating balance and postural control, the clinically-relevant outcome would be patients' reported falls. A 24.2 % post-operative falls' rate for TKR patients was reported up to one year by Swinkels & Allain, (2013) and Swinkels *et al*, (2009), compared to 40 % reported by Levinger *et al*, (2012). Current estimates of falls for community dwelling older people have reported a 30 % - 33 % (O'Loughlin *et al*, 1993; Morris *et al*, 2004). The difference between falls rate for the 12 months following surgery between the study by Levinger *et al*, (2012) (40 %) and the 24.2 % reported by Swinkels *et al*. (2009) was not clear. It may be related to the different definition of falls used in each study. Swinkels *et al*, (2009) excluded falls that were a result of a major intrinsic event, whilst the study by Levinger *et al* (2011 & 2012) reported falls due to trips and loss of balance but not necessarily directly linked to

the operated limb. Due to the presence of pain and neuromuscular deficits associated with TKR, it is possible that these factors may play a greater role in increasing the risk of falls post-surgery. The rate remained as high as 40 % - 45.8 % for individuals identified as fallers prior to surgery (Swinkels *et al*, 2009; Levinger *et al*, 2012). Nevertheless, there was a significant switch of fallers' pre-TKR who became non-fallers after TKR (54.2 %); however, the number of falls for the whole year prior to the surgery was not reported (Swinkels *et al*, 2009). At least one fall in the first year post-TKR was recorded for 48 % of the surgical group compared with 30 % of the control group (Levinger *et al*, 2011). Following TKR, there was a 27 % reduction in the number of patients exceeding the cut-off point of 14s in the TUG Test (Swinkels & Allain, 2013; Swinkels *et al*, 2009). This time-related cut-off point has been proposed as a criterion for ruling out a high risk of falls in older adults (Shumway-Cook, *et al*, 2000). Therefore, although the likelihood of falls seems to decrease after TKR, there is still a considerable amount of falls recorded post-TKR.

Control of balance is dependent upon both static and dynamic components (Hill *et al*, 2013; Morrow *et al*, 2010) and should therefore be tested accordingly, although falls usually occur during an active task. Bilateral postural responses after perturbation differ between TKR patients and age-matched controls. These differences are observed, not in the displacement of Center of Pressure (COP) or Centre of Mass (COM), but in muscle activation latency in muscles acting on the knee (gastrocnemius, rectus femoris, vastus lateralis and biceps femoris) and in subsequent kinematics of the knee joint (reduced knee extension), suggesting a central postural re-organisation process to protect against overly stressing the joint (Gage *et al*, 2007; 2008; Mandeville *et al*, 2008; Venema *et al*, 2012; Viton *et al*, 2002; Yakhdani *et al*, 2010). During walking, variability in knee kinematics is reduced and local dynamic stability again seems to be gradually restored (Yakhdani *et al*, 2010).

Therefore, the mild improvements observed in dynamic balance following TKR, may result from the retensioned capsuloligament structures and reduced pain and inflammation (Cho & Hwang, 2012; Swanik *et al*, 2004). Patients post-operatively tend to normalise their weight distribution and develop more symmetrical posturo-motor control, increasing their success rate. However, the strategies adopted pre-operatively do not seem to recover when compared to age-matched controls

(Mandeville *et al*, 2008; Mauer *et al*, 2005; Viton *et al*, 2002). No study compared TKR patients with non-TKR patients with similar severity of knee OA and equivalent health status. Therefore, physiotherapy programmes should involve patients training pre- and post-TKR in using strategies to achieve symmetrical weight-distribution, in standing and during dynamic tasks. Preliminary evidence on movement and weight' distribution symmetry training, via the use of biofeedback, was recently introduced in the literature (Zeni *et al*, 2013).

Several studies identified methods to assess balance either with highly sophisticated equipment or with simple clinical tests associated with physical performance. Examples of the latter include single leg standing balance (SLSB), TUG Test or Berg Balance scale (Mauer *et al*, 2005; Swinkels *et al*, 2009; Swinkels & Allain, 2013). Postural sway is often used as an indicator of static standing balance (Cho & Hwang, 2012), where bodily movement in both the antero-posterior (AP) and lateral direction is analysed, usually by the use of a force-platform. Eleven studies used highly sophisticated equipment such as force-plates to assess the balance performance of patients. Balance systems or sway-meters were used from four studies either with single- or double-leg stances. Functional tests such as TUG and scales such as the WOMAC (as indirect measures of balance), were used in several studies with improved scores of 2.5 - 8.3s ($p = 0.001$) for the TUG and around 5 units of improvement for the WOMAC index (60.2 ± 6.9 pre-operatively vs 55.1 ± 12.5 post-TKR) (Cho & Hwang, 2012; Levinger *et al*, 2011; Mandeville *et al*, 2008; Schwartz *et al*, 2012; Swinkels & Alain, 2013). All the outcome measures used have been previously validated and have shown moderate to high reliability (ICC: 0.59 - 0.97).

Implications for clinical practice

Clinically, from a surgery perspective, surgically correcting knee joint alignment and specifically varus deformity post-TKR has been shown to improve balance (Cho & Hwang, 2012). Considering the catastrophic consequences of peri-prosthetic fractures after a patients' fall, 3D evaluations of the alignment and computer-assisted gap-balancing techniques, compared to conventional techniques of TKR, may produce more advantageous balance effects (Kim *et al*, 2011; Pang *et al*, 2011). The clinical relevance regarding rehabilitation is that patients' training should involve rehabilitative strategies in static and dynamic tasks to achieve symmetrical

weight-distribution, implemented both pre- and post-TKR. Interestingly, movement and weight distribution symmetry training, via the use of biofeedback, was recently introduced in the literature (Zeni *et al*, 2013). At the moment, there is only preliminary evidence to underpin the use of targeted sensori-motor elements within a physiotherapy programme (Piva *et al*, 2010; Liao *et al*, 2013). Bilaterally observed impairments indicate that rehabilitation should include balance exercises involving both single- and double-leg stances to provoke overload and adaptation and prevent falls. Balance perturbation tasks can be more targeted towards frontal plane provocation and less in the sagittal plane, by enhancing knee and ankle balance recovery strategies (Gage *et al*, 2007; Gage *et al*, 2008). Moreover, knee strength and proprioception showed statistically significant improvements after TKR, whereas postural sway with eyes open and reaction time did not (Levinger *et al*, 2011; Levinger *et al*, 2012). Therefore, according to the findings from the studies, physiotherapy programmes should mostly incorporate the influential factors of falls (i.e. muscular strength performance associated with the knee, proprioception and balance exercises with eyes closed). Finally, it would be interesting to know in a next stage whether an exercise programme is acting additively or interactively with the effects of TKR surgery towards achieving better functional mobility, sensori-motor and balance performance.

Several limitations need to be considered when interpreting the findings of this review. The research question included the components of PICO, however not all studies included a comparator group. The researcher used a comprehensive literature review strategy, searched in more than two databases and searched the reference list of included papers but did not consult experts in the field. Moreover, this systematic review was restricted to studies only published in the English language. Due to methodological flaws across the studies, the level of evidence was not high enough to allow for the generalisation of results. More cohort studies with robust methodologies are needed to investigate the effect of TKR on balance and falls' incidence. Finally, the researcher used the CASP scale for assessing the risk of bias of selected studies as a valid, novice-friendly tool. Although the online courses on how to undertake systematic reviews according to the Cochrane Library were taken, the corresponding method and scale was not followed due to associated financial constraints. Because of the methodological heterogeneity across the study designs (i.e. in methodological outcome measures and timing of

measurements), results from a potential meta-analysis (with an $I^2 > 85\%$) would not have added evidence that was consistent. Furthermore, due to methodological flaws across the studies, the level of evidence was not high enough to allow for the generalisation of results. More studies with robust methodologies are needed to investigate the effect of TKR on balance and falls' incidence.

5.5 Conclusions

The findings of this systematic review provide moderate evidence to support that TKR influences dynamic balance positively for up to one year following surgery. Controversial are the findings amongst studies regarding single limb standing balance, where four studies conclude with a significant improvement after TKR and two studies show no difference. However, both static and dynamic balance (in the frontal plane) remains impaired compared to age-matched controls. Moreover, indefinite are the findings as to whether people after TKR actually report reduced or the same number of falls (Level of evidence II-IV). However, the incidence of falls (40% - 48%) remains higher than that of community age-matched controls (30% - 33%). Potentially beneficial effects can be reported regarding the fear of falling. Patterns of change (acute and chronic) and congruence amongst the interpretation of findings from the reviewed papers, endorse a conceptual framework for the knee undergoing TKR surgery. The framework related to falls' risk parameters supports that knee extension strength, proprioception deficits and compensatory postural strategies are persisting after surgery and are acting as the potential factors contributing to why the capability for balance and the avoidance of falls might be linked and only partially restored after TKR.

Chapter 6

What is the effect of sensori-motor training compared to usual care on functional outcome and balance performance of patients' undergoing TKR?

A systematic review.

Abstract

Background and Purpose: Total knee replacement has a beneficial effect on patients' functional ability. However, incidence of falls and proprioceptive deficits are not restored even one year after surgery (Levinger *et al*, 2012; Schwartz *et al*, 2012; Swinkels *et al*, 2012). Early and intensive exercise post-TKR has received limited endorsement in the literature and without critical evaluation of dose and type. The aim of this review was to systemically identify and critically appraise clinical studies investigating the effect of sensori-motor training (SMT) on functional performance and balance in TKR patients.

Methods: The electronic databases Cochrane Library, MEDLINE, EMBASE, CINAHL, PEDro and the register of current controlled trials were searched up to September 2014. The MEDLINE Mesh keywords used were: Balance OR stability OR postural control OR proprioception OR sensori-motor AND exercise OR training OR rehabilitation OR physiotherapy OR physical therapy AND knee replacement OR knee arthroplasty in the title or abstract or keywords of the studies Two independent reviewers used pre-defined inclusion and exclusion criteria to identify all eligible articles. Eligible articles were summarised and critically reviewed, using the PEDro Scale.

Results: Two hundred and seventy six articles were screened, six were included. The studies presented the results of 409 patients (269 intervention, 140 control). A range of rehabilitation protocols were defined by components of proprioception, postural control, balance perturbation and coordination. All studies supported the use of SMT as an additional element in patients' rehabilitation protocols. The evidence showed that functional ability and balance were improved compared to controls and this was more prominent when assessed using clinical performance-based tests compared to patient-reported scales. However, generalisation of findings is limited because of a lack of acceptable effect size combined with underpowered experimental designs in some studies; thus, suggesting the possibility of either a lack of potency of intervention or a compromised capability to detect subtle gains that might have been offered by the intervention.

Conclusions: Limited robust (1a) evidence supports the equal effectiveness of contemporary practice and enhanced functional rehabilitation with SMT for patients

post-TKR for improving functional capabilities. However, dose-response thresholds of exercise eliciting improvement warrant further investigation.

6.1 Introduction

Motor and sensory deficits associated with knee joint degeneration have been recognised in knee OA patients, altering gait, balance and postural control, and therefore likely to be increasing the risk of falls (Lytinen *et al*, 2010; Sibley *et al*, 2015). Approximately 60 % - 80 % of knee OA patients report knee instability, which affects sensori-motor and postural control, incidence of falls and ability to perform ADL (Fitzgerald *et al*, 2011; Lytinen *et al*, 2010; Messier *et al*, 2000; Schmitt *et al*, 2008).

Evidence from the systematic review of the previous chapter (Chapter 5) investigating the effect of TKR as a treatment to knee OA, in restoring the balance performance and incidence of falls of patients showed some improvement in dynamic balance and controversial findings regarding static balance and number of falls. Posturomotor strategies although seemed to improve post-TKR, remained impaired compared to age-matched controls up to one year post-surgery. There is a 27 % post-surgery reduction in patient' numbers exceeding cut-off criteria for falls-risk compared to pre-surgery in the elderly (a TUG score of ≥ 14 s has been used to identify individuals at higher risk of falling), indicating that falls-likelihood and restrictions to QoL, is reduced but not eliminated (Schwarz *et al*, 2012; Swinkels *et al*, 2009; Swinkels & Allain, 2013). The literature has showed that the high prevalence of falls was predominantly attributed to muscle weakness, proprioception deficits, and reaction time in postural sway tasks (Mandeville *et al*, 2008; Schwartz *et al*, 2012), and not to balance-related confidence, as the latter had been generally improved. Thus, the persistent deficits necessitate early and targeted rehabilitation (Cho & Hwang, 2012; Levinger *et al*, 2011; Mandeville *et al*, 2008; Moffet *et al*, 2004; Silva *et al*, 2012; Valtonen *et al*, 2009). No study has investigated whether exercise programmes act additively or interactively to the observed effects of TKR.

Studies investigating traditional 'cornerstones' of TKR recovery involving exercise programmes consisting of ROM and strengthening exercises, have shown small beneficial effects of functional abilities whereas functional rehabilitation has elicited enhanced physical performance outcomes but presented an improvement plateau at 3 - 6 months (Bade *et al*, 2011; Moffet *et al*, 2004). Studies investigating the effects of TKR and relevant conventional exercise programmes showed some improvement

in sensori-motor performance, without again however full recovery being achieved up to one year post-surgery (Bascuas *et al*, 2013; Bakirhan *et al*, 2012; Wada *et al*, 2002; Swanik *et al*, 2004). Functional rehabilitation augmented by targeted SMT could potentially address these deficits and offer improved physical activity, postural control and prevention of falls. Importantly, proprioceptive rehabilitative training demonstrated efficacy for balance performance in patients with OA of the knee (Mat *et al*, 2015; Silva *et al*, 2012). Sensori-motor training has been found to improve proprioception, strength, and postural stability in lower extremity rehabilitation (Fitzgerald *et al*, 2002; Mat *et al*, 2015; Pavlu & Novosadova, 2001; Zech *et al*, 2009). Balance and proprioception training has been characterised as SMT, first developed by Dr. Vladimir Janda, as part of a treatment approach to chronic musculoskeletal pain syndromes. A recent systematic review investigating the effect of physical exercise after TKR focused on some studies that had included evaluation of programmes of SMT (Pozzi *et al*, 2013). The review showed that sensori-motor training could serve as a novel and clinically appropriate rehabilitation refinement to traditional approaches in TKR patients (Pozzi *et al*, 2013). Nevertheless, its dose-response characteristics of time, frequency and volume have not been clarified.

A special form of therapeutic exercise designed to address not only isolated strengthening of a group of muscles, but also to enhance CNS' function for regulating movement and proper muscular firing patterns for maintaining joint stability, is characterised as SMT (Rienmann & Lephart, 2002 a; b) (please refer to Chapter 2, section 2.6, page 30). Functional training is a classification of exercise that involves training the body for the ADL (such as walking, chair rising). Sensori-motor training, through the balance component challenges, is thought to stimulate afferent information of joint sensors and therefore, influence muscle activity and the neuromuscular control scheme (Rienmann & Lephart 2002b). The destabilising loads to which patients are exposed, help the neuromuscular system adapt to conditions that may induce knee instability during ADL. It has been demonstrated that with the practice of a certain movement task, muscle activity patterns shift from generalised co-contraction of agonist/antagonist pairs to well-timed selected bursts activity of the pairs and thus, more coordinated agile and skilled performance, specific to the field being learned (Thoroughman & Shadmher, 1999). Balance perturbations can arise from events such as slips, trips and collisions, but also occur as a consequence of volitional movement (e.g. turning, bending, reaching). For

example, change-in-support balance reactions, which involve very rapid limb movements (stepping, or reaching to grasp an object for support), play a critical role in responding to balance perturbations. These compensatory stepping and grasping reactions are the only line of defense against large perturbations, but are also frequently recruited at lower magnitudes of perturbation (provided that subjects are permitted to react naturally) and are produced through coordinated neuromuscular activity.

Components of balance and proprioception usually include weight-bearing (full or partial) exercise aiming to perturb balance and knee stability such as quick stops, turns, changes in direction, retro-walking, side-walking, overcoming obstacles, exercise on wobble boards and generally challenges that may be encountered during ADL (Ahmed, 2011; Fitzgerald *et al*, 2011). Overall physical function might be further improved if individuals were better prepared to deal with these challenges to motor function. This improvement in overall physical function might be accomplished if individuals were exposed to the latter challenges in motor function in conjunction with contemporary impairment-based exercise therapy programmes.

From the analysis of the available literature in knee OA, it was evident that SMT produces significant improvements in balance and functional performance. Nevertheless, it was important to know how patients respond to such forms of training post-operatively following TKR. Moreover, important questions such as components of SMT added to the usual functional physiotherapy regime, timing of initiation, and intensity/numbers of exercises and parameters influencing effectiveness, are essential to be clarified for safe and effective implementation.

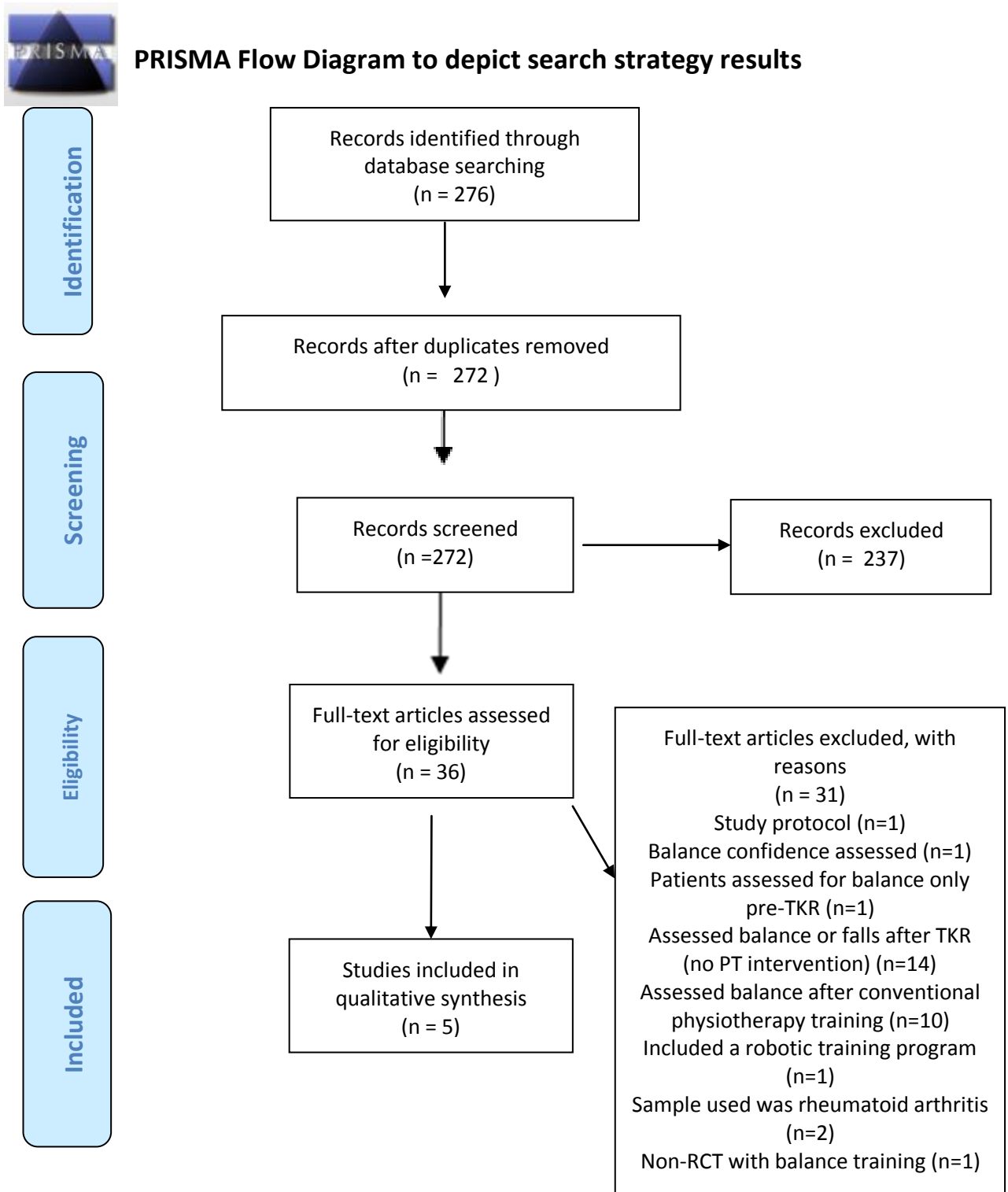
The aim of the current systematic review was to analyse all published RCTs that have included sensori-motor components in the physiotherapy programme in patients following TKR, in order to assess the latter's effect on functional performance, pain relief and balance' performance compared to usual care. Moreover, potential answers to further important questions, such as the timing of when to best initiate such a programme, as well as the optimal volume of balance-related exercises to be added to usual contemporary physiotherapy programmes, were evaluated.

6.2 Methods

6.2.1 Search Strategy

The electronic databases: the Cochrane Central Register of Controlled Trials (Cochrane Library), MEDLINE, EMBASE (via ProQuest), Biomed Central, Cinahl (via EBSCO host) and Physiotherapy Evidence Database (PEDro) were searched from 1995 to December 2014 (Figure 6.1). The MEDLINE Mesh keywords used were: Balance OR stability OR postural control OR proprioception OR sensori-motor AND exercise OR training OR rehabilitation OR physiotherapy OR physical therapy AND knee replacement OR knee arthroplasty in the title or abstract or keywords of the studies. Randomised controlled trials were only included if published in the English language. The reference lists of all eligible papers were also screened to identify any studies missing from the electronic searches.

Figure 6.1 Prisma Flow Diagram to depict search strategy for systematic review.



6.2.2 Eligibility Criteria

Eligibility assessment was performed independently in a standardised manner and disagreements amongst reviewers were resolved by consensus. Therefore, studies were included if they fulfilled the following five criteria:

1. Participants underwent primary TKR.
2. An exercise-based intervention incorporating sensori-motor components was involved compared or not with another therapeutic intervention, placebo or control.
3. Balance and/or functional performance was/were used as outcome measure(s).
4. Study design was a randomised design.
(http://cccr.org/cochrane.org/sites/cccr.org/cochrane.org/files/uploads/Study_design_guide2013.pdf).
5. The full paper was published in the English language.

All cadaver or animal studies were excluded. Moreover, studies with samples involving patients with rheumatoid arthritis (RA) were excluded.

6.2.3 Study identification

Two evaluators independently selected the studies based on titles and abstracts, excluding those not related to the subject. The full text was obtained for all papers that were considered potentially relevant. Once collected, these were assessed by both reviewers to determine if eligibility criteria had been fulfilled. The studies finally included were described and analysed according to a certain structure: author/year, sample, study design, assessment outcome measures, timeline, physiotherapy treatment, equipment and effects. Each reviewer assessed the methodological quality of the included studies independently, using the PEDro scale.

An independent statistician (RR) of the QM University was consulted by the researcher (MM) to examine the possibility of a potential meta-analysis by collating data from the studies. Two options of potential meta-analysis were investigated. The first option collated data regarding the research question of how components of sensori-motor training compared to usual care influence functional outcome of patients undergoing TKR. The second option collated data for investigating the

research question of sensori-motor components compared to usual care influence the balance performance of patients undergoing TKR.

6.2.4 Critical appraisal

Since all studies were RCTs included in PEDro, this scale was considered more appropriate (than CASP scale used in the Systematic review of Chapter 5) as it is a high quality scale within the physiotherapy profession, with studies being scored by independent researchers. Therefore, studies were analysed for methodological quality by the PEDro scale for trials (http://www.pedro.org.au/english/faq/#question_five) that gives a score out of 10 according to a number of specific criteria met. Trials are rated according to the checklist. The PEDro scale considers two aspects of trial quality, internal validity of the trial and whether the trial contains sufficient statistical information to make it interpretable. To assess internal validity, a number of criteria were used, including random allocation, concealment of allocation, comparability of groups at baseline, blinding of patients, therapists and assessors, analysis by intention to treat and adequacy of follow-up. To assess interpretability, between-group statistical comparisons and reports of both point estimates and measures of variability are rated. This gives a total of ten scale items.

6.3 Data Analysis

In the first stage, a descriptive review of studies incorporating a physiotherapy programme with components of sensori-motor training in patients after TKR, was undertaken (Table 6.1).

In the next stage, the analysis involved a critical appraisal process of the studies according to the PEDro scale's determination of the methodological quality of the included studies (Table 6.2).

All data extracted from the studies were analysed independently by each reviewer (MM and RP) and subsequently discussed. In any case of disagreement, further discussion was performed with a third reviewer (NG) to reach a mutual agreement.

Table 6.1 Description of studies including SMT programmes in TKR patients.

Study	Sample	Age (years)	Intervention	Dose	Intensity Progression	Setting	Start of programme	End of programme	Main outcome measures	Final follow-up	Results	Clinically sig. effects for balance & function with SMT
Fung et al, 2012	IG n=27 (19F) CGn=23 (14F)	68	IG: PT+ Wii-Fit balance challenging CG: PT+ Strengthening, posture exercises	60min PT+15 min Wii fit Frequency/ Duration (weeks) NS	Exercise progressed	Outpatient clinic-supervised	Average 37 days after surgery	Average 54 days after surgery	Active ROM;2MW T; NPRS; LEFS; ABCS; LOR	~54 days after surgery	No stat.sig. between groups	Medium ES (0.5) for function (LEFS) for IG group ($p = 0.07$). 15 % greater balance confidence (ABCS) for IG vs CG.
Gsoettner et al, 2011	IG n=18 (16F) CG n=20 (14F)	IG:73; CG:67	IG: Proprioceptive training + walking, stretching CG: NS	Daily for 45 min (15 min standard + 30min proprioceptive)	Exercise progressed	Home-based program; supervised once a week at clinic	6 weeks pre-op.	At time of TKR	Balance OSI (bilateral stance), Gait Speed Timed Stair test, WOMAC, KSS	6-weeks after surgery	Stat sig. improvement ($p<0.05$) in balance and function over time for both IG and CG post-TKR. Stat sig. improvement in balance (OSI) between groups favouring IG ($p< 0.05$): OSI mean (SD): CG: 3.4 (0.9)	Greater improvement in balance, not function with SMT 6 weeks post-TKR.

**Liao et al,
2013**

IG n=58
(46F)
CG
n=55
(37F)

IG: 73;
CG: 71

IG:
Functional+
Balance
training
CG: Functional
training

90min (30min
Functional+60
min balance;
Frequency NS

Exercise
progressed

Outpatient
clinic-
supervised

At least 2
months after
surgery

8 weeks

FRT;
SLST;
10MW;
TUG,
30SCR,
WOMAC

8
weeks
after
start
progra
m

pre-op to 2.9
(0.7) 6 weeks
post-op vs IG:
3.1 (1.4) pre-
op. to 2.2 (0.7)
6 weeks post-
op.

Stat. sig.
improvement
($p < 0.001$) for
IG vs CG.
WOMAC: CG:
77.2 (5.0) pre-
op. to 42.9
(9.9) post-op.
vs IG: 75.5
(5.2) pre-op. to
36.5 (9.0);
TUG: CG: 12.4
(1.5) pre-op. to
10.7 (1.0) vs
CG: 12.9 (1.5)
pre-op. to 9.9
(0.9);
SLST EO: CG:
4.5 (0.9) pre-
op to 7.2 (1.0)
vs IG: 4.6 (0.8)
pre-op to 8.7
(0.8).

Greater
Improvement
in function and
balance with
SMT

Liebs et al, 2012	IG n=66 CG n=69	IG: 68.5 CG: 70.9	IG: early aquatic therapy CG: late aquatic ther. Aquatic: (proprioception, coordination, strengthening) + land-based PT programme (balance, coordination, gait).	3/week for 30min balance+ daily PT	NS	Clinic-based supervised	IG: 6th Post-op day; CG: 14th Post-op day	up to 5 weeks	WOMAC; SF-36,	24 months	Not statistically significant. Mean outcomes favouring IG. WOMAC Baseline to 24m post-TKR: IG: 57.1 (21.4) to 13.8 (13.6) CG: 54.8 (22.7) to 20.7 (21.3).	Small ES for function (ES=0.2-0.4 in WOMAC). Clinical sig WOMAC at 24m: 6.9 units (with a MCID=5.3).
Piva et al, 2010	IG n=18 (13F) CG n=17 (12F)	IG: 70 ; CG: 67	IG: Functional+ Balance training CG: Functional training	12 sessions of 90min (30min functional, 60min balance) + Home based programme for 4 months (2/week)	Exercise progressed	Clinic-based supervised	2-4 months after surgery	6 weeks after start programme	Gait speed; SLST, 10MWT; TUG, 30SCRT, WOMAC, LEFS	6 months	Within group mean change (95 % CI) WOMAC: IG: -5.2 (-8.4 to -1.9) CG: -8.1 (-12.6 to -3.6). Gait speed: IG: 0.09 (0.02 to 0.2) vs CG: -0.01 (-0.08 to 0.06). SLS: IG: 4.0 (-1.4 to 9.4) CG: -0.7 (-3.2 to 3.2 to 1.8).	Clinically sig effects in function (gait speed: 0.1m/s, WOMAC) and balance (SLS) favouring IG

CG = Control group; IG = Intervention group; EO: eyes open; NS= not stated; PT = Physiotherapy; op.: operated; ROM=range of motion; LEFS=lower extremity functional scale; MWT= min walk test; OSI: Overall stability Index; SLST= single limb standing time; SCRT=; Stair Climb Rise test; FRT=functional reach test; LOR=length of outpatient rehabilitation; KSS=Knee society score.

6.4 Results

A total of 276 citations were identified from the search strategy, summarised in Figure 6.1. In the initial search, 237 studies were eliminated because the title, abstract or keywords did not match the proposed theme. The excluded studies involved studies measuring soft-tissue balance (length and tension relationships from ligaments and/or capsule that affect joint alignment achieved intra-operatively), or balance of the prosthesis as a result of the surgery technique, either intra-operatively or post-operatively with X-ray, or other medical examinations. Of the 39 studies that remained, twenty-four were eliminated due to: a) having used non-English language, b) having assessed balance performance without and intervention, or c) having used other sample comorbidities such as RA, or cadaver samples. Ten studies were excluded as they had assessed balance and falls following a conventional physiotherapy programme, but without the studies having incorporated SMT. Therefore, five studies were deemed eligible and were finally included in the review (Figure 6.1). The results of the critical appraisal according to PEDro scale are presented in Table 6.2.

Table 6.2 PEDro scale score for RCTs including SMT in patients following TKR.

PEDro SCALE	Fung et al, 2012	Gsoettner et al, 2010	Liao et al, 2013	Liebs et al, 2012	Piva et al, 2010
Eligibility criteria specified	Yes	Yes	Yes	Yes	Yes
Random group allocation	Yes	Yes	Yes	Yes	Yes
Concealed allocation	No	Yes	Yes	Yes	Yes
Baseline comparability	Yes	Yes	Yes	Yes	Yes
Blind Subjects	No	No	No	No	No
Blind Therapists	No	No	No	No	No
Blind Assessors	Yes	No	Yes	No	Yes
Adequate follow-up	Yes	Yes	Yes	Yes	No
Intention-to-treat Analysis	No	No	No	Yes	No
Between group comparisons	Yes	Yes	Yes	Yes	Yes
Point estimates and variability	No	Yes	Yes	Yes	Yes
Total Score (/10)	5	6	7	7	6

6.4.1 Participants

Patients had primary OA (grade III-IV, Kellgren and Lawrence system) (Kellgren & Lawrence, 1957) and fulfilled criteria to undergo TKR (same prosthesis; cemented; cruciate retention). The five studies included 371 subjects (187 randomised and allocated to the intervention; 184 to a control group).

6.4.2 Outcome measures

All studies used validated measures (Sibley *et al*, 2015) to assess balance in the absence of 'gold standard' criteria. Parameters used were static or dynamic balance during either single or double leg stance, or during a functional task. Patient-reported outcomes including the Activity-specific Balance Confidence Scale (ABC-S), had been used (Fung *et al*, 2012). Sophisticated equipment (force plates; balance-platforms [Biodex stability system]) measuring postural sway, center of mass (COM) transference, bilateral dynamic stance (Gstoettner *et al*, 2011), or center of pressure (COP), were used, as well as assessments of gait speed and function (WOMAC, Knee society score [KSS], Lower Extremity Functional Scale [LEFS], SF-36) (Fung *et al*, 2012; Gstoettner *et al*, 2011; Liao *et al*, 2013; Liebs *et al*, 2012; Piva *et al*, 2010), clinical functional outcomes (TUG Test, Functional Reach Test (FRT), single leg stance (SLS), and the stair climb test (SCT) (Liao *et al*, 2013; Piva *et al*, 2010).

6.4.3 Sensori-motor interventions

Piva *et al* (2010) and Liao *et al* (2013) implemented conceptually similar and previously tested for effectiveness (Pozzi *et al*, 2013), protocols of functional exercise training, but enhanced with SMT (Levinger *et al*, 2011; Swanik *et al*, 2004; Valtonen *et al*, 2009). Protocols involved six weeks and eight weeks supervised programmes, respectively, with the study by Liao *et al* (2013) involving a subsequent four months home programme. The above mentioned two studies (Liao *et al*, 2013; Piva *et al*, 2010), and the study by Gstoettner *et al* (2011), had focused on balance exercise training involving agility and perturbation techniques (side walking, cross-over steps, single leg standing). Others had enhanced usual physiotherapy care by utilising Nintendo Wii-fit game platform-based exercises to engage lateral weight shifting, multidirectional balance and static/ dynamic postural control (Fung *et al*, 2012), or by using full weight-bearing functional and proprioceptive exercises, mimicking ADL (Gstoettner *et al*, 2011; Liao *et al*, 2013;

Piva *et al*, 2010), or by aquatic exercise aiming at training proprioception, coordination, and strengthening (Liebs *et al*, 2012).

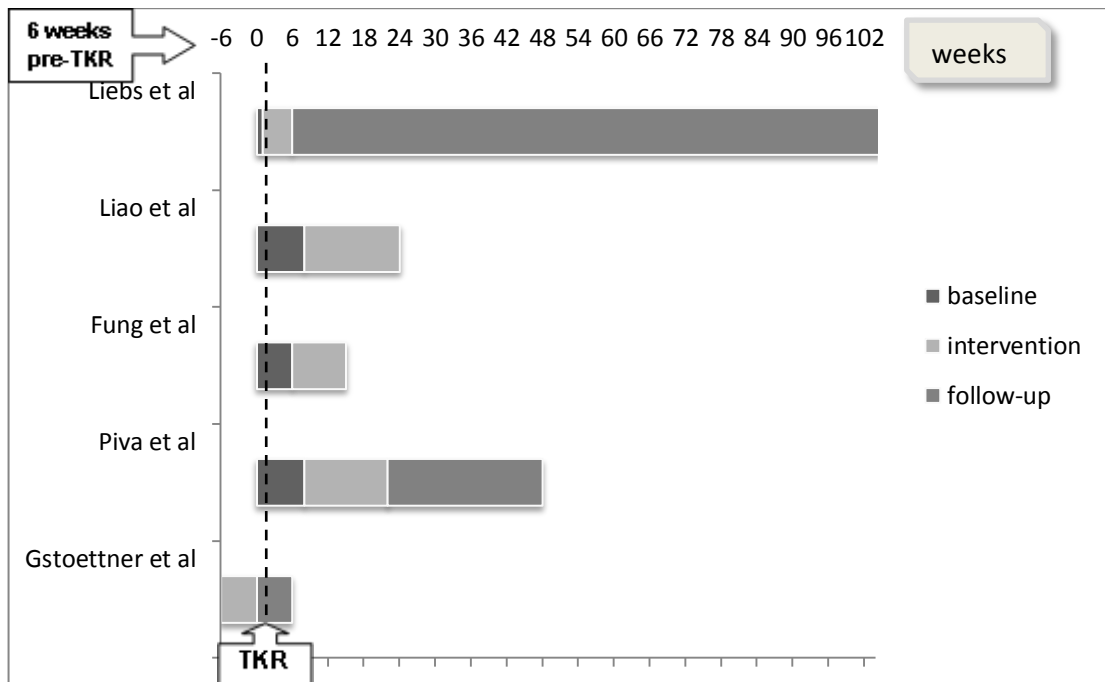
6.4.4 Timing of initiation

Some studies have started implementing SMT at least two months post-operatively, in order to ensure pain and effusion elimination (Fung *et al*, 2012; Liao *et al*, 2013; Piva *et al*, 2010), others incorporated sensori-motor elements within days of surgery using land or aquatics programmes (Liebs *et al*, 2012), or even, pre-operatively (Gstoettner *et al*, 2011). Notably, all pre- and post-surgery TKR interventions were tolerated well by patients, with no adverse effects reported.

6.4.5 Volume-duration of exercise

In the previously described studies by Piva *et al* (2010) and Liao *et al* (2013) that had shared a common format of delivery, the volume of exercise implemented in control and intervention groups was not equal, with the intervention group receiving 30 minutes more training in each session. By contrast, the study by Fung *et al* (2012) was iso-volumetric across groups (60 + 15 minutes (standard + SMT) but did not report the frequency of sessions undertaken by each group. Non iso-volumetric training was noted in the study by Gstoettner *et al* (2011), in which the intervention group's, six weeks, six sessions pre-habilitation programme (45 minutes session duration) had not been matched by the control group. Similarly, the study by Liebs *et al* (2012) reported earlier initiation (by several days) of post-TKR surgery conditioning for the intervention group compared to controls (6th vs.14th post-operative day). The time-line of each of the included studies, in terms of baseline measurement, intervention period and follow-up are presented in Figure 6.2.

Figure 6.2 Time-line of studies, base-line measurement, duration of intervention and final follow-up.



Baseline: Admission period
 Intervention: Training period before or after TKR
 Follow-up: period after intervention that patients' post-test final study evaluation was conducted.

6.4.6 Exercise progression

Criteria for patients' exercise progression (via re-assessment) were not detailed within the studies. Progression for patients had been regulated by precedent of successfully completing similar exercises during prior physiotherapy (Fung *et al*, 2012), without experiencing increased pain, effusion, giving-way and decreases in ROM (Gstoettner *et al*, 2011), or by clinical review of their capabilities (Piva *et al*, 2010). In several studies (Liao *et al*, 2013; Liebs *et al*, 2012), no progression was reported throughout the rehabilitation period.

6.4.7 Follow-up

Most of the studies followed-up patients for two to six months after surgery (Fung *et al*, 2012; Gstoettner *et al*, 2011; Piva *et al*, 2010; Liao *et al*, 2013), apart from the study by Liebs *et al* (2012) which had followed-up patients for up to two years post-operatively.

64.8 Effects on pain and function outcome measures

The study by Liebs *et al* (2012) showed that early compared to late initiation (6th vs.14th post-operative day) of aquatic SMT combined with a land-based functional and balance programme led to superior improvements in function and QoL (mean scores in WOMAC at two years follow-up), however differences did not achieve statistical significance (Liebs *et al*, 2012). Liao *et al* (2013) showed statistically significant change scores (between 36 %-50 %: WOMAC and functional tests such as TUG, stair-climb test, functional reach test) for an eight week programme (n = 113) of additional balance exercises alongside functional training compared to a programme of functional training solely. Over a shorter intervention (six weeks), Piva *et al* (2010) in a study using the same intervention groups as the study by Liao *et al* (2013), showed no statistically significant change scores, however with an underpowered feasibility study design (n = 43),. Similarly, Gstoettner *et al* (2011) showed no inter-group (proprioceptive training versus control group) differences on function (WOMAC and KSS) after pre-habilitation. However, inter-group differences were noted with the SMT group showing superior improvement after TKR. Fung *et al* (2010) showed equivalent improvement in pain and functional performance (NPRS and LEFS) between the usual care group and the group with the additional Wii-Fit training, almost two months after TKR, again with an underpowered pilot design study..

6.4.9 Effects on balance' outcome measures

Augmentation with balance exercises elicited ~25 % post-surgery improvements in single limb standing balance stance (SLSB) compared to baseline (Liao *et al*, 2013; Piva *et al*, 2010), 15 % gains in patients' balance confidence compared to controls (Fung *et al*, 2012), and statistically significant ($p<0.05$) post-surgery gains in bipedal stance performance with pre-habilitation compared to controls (Gstoettner *et al*, 2011).

6.4.10 Summary descriptive results collated for meta-analysis

Two options of potential meta-analysis were investigated. The first option collated data regarding the research question of how components of sensori-motor training compared to usual care influence functional outcome of patients undergoing TKR. The second option collated data for investigating the research question of sensori-

motor components compared to usual care influence the balance performance of patients undergoing TKR.

The quality of the studies was assessed in the next stage as although all studies satisfied criteria for inclusion, their methodologies varied substantially.

6.4.11 Critical appraisal of studies' methodological quality

Table 6.2 presents critical appraisal of all studies (PEDro). All studies offered adequate robustness in methodology (PEDro: 5 - 7) with clearly defined research questions, population' characteristics and methods of assessing balance.

All studies included had provided clear sampling descriptions (numbers, age, gender and pathology), acceptable recruitment methods and rates of loss-to-follow-up. A recurrent limitation was that apart from the study by Liebs *et al* (2012) producing a small to moderate effect size (up to 0.39), no other study had used experimental design sensitivity criteria to compute sample size' requirements. The studies by Liao *et al* (2013) and Gstoettner *et al* (2011) provided statistically significant improvement between groups in some of the outcome measures tested, without however, reporting effect sizes. The study by Piva *et al* (2010) was labeled as a 'pilot', and had lacked a significant treatment effect, or it had been potentially underpowered. Similarly, the study by Fung *et al* (2012), having been underpowered potentially, offered high rates of retention of null-hypotheses (inflated type-II error).

6.5 Discussion

Results from this systematic review suggest that SMT induces superior balance performance up to six months post-TKR compared to usual care in OA patients (Gstoettner *et al*, 2011; Liao *et al*, 2013). Improvement in functional outcomes was not unanimously reported by all studies as only the study by Liao *et al* (2013) supported this finding whereas the rest of the studies showed a trend towards greater improvement, without however managing to show statistical difference between groups. Nevertheless, the findings of two of the studies were limited by the underpowered design (Piva *et al*, 2010; Fung *et al*, 2012) and have provided the appropriate power of the sample needed for further studies of this context. The collated information from all studies however, showed for the first time in OA

patients undergoing TKR surgery that SMT is an acceptable adjunct to usual care in physiotherapy with no adverse effects.

The studies by Liao *et al* (2013) and Gstoettner *et al* (2011) favoured SMT. Both studies showed a greater effect of additional SMT compared to the usual care on balance and persistent functional deficits, bridging a potential gap in rehabilitation programmes. Moreover, studies report SMT as a therapeutic intervention which is entertaining for patients (Liebs *et al*, 2012), is independent of specialised equipment (e.g. Wii fit) and environment (e.g. land or water-based), has the capability of producing movements with less energy expenditure (promoting functional and metabolic benefits) (Ageberg *et al*, 2009; Viton *et al*, 2002) and importantly, offers no adverse effects to patients in any of the studies reviewed. However, considerable variability was observed in the methodological designs of the included studies, precluding definitive conclusions.

Exact mechanisms underpinning how TKR impacts on the performance of mechanoreceptors remains elusive. The reviewed studies suggested mild improvements in balance following TKR (Gstoettner *et al*, 2011; Liao *et al*, 2013). These kinds of additional sensori-motor interventions activate proprioceptors in the ankle and hip joint, as well as proprioceptors in muscular, tendon and ligament tissues (e.g. PCL) at the knee, since articular proprioceptors have been resected during TKR. These improvements may also result from retensioned capsuloligament structures (e.g. collateral ligaments), and reduced pain and inflammation in the knee joint following the surgery (Liebs *et al*, 2012). Moreover, gradual functional and SMT rehabilitation conditioning after TKR induces restoration to intra-sensory proprioceptive compensation either at the knee or other joints (hip/ankle) (Gauchard *et al*, 2010). Therefore, corrective compensatory strategies regulate better postural control through neuroplasticity, involving improved muscle activation synergies, movement patterns, joint torques and contact forces that are disturbed during OA degeneration (Gauchard *et al*, 2010; Ageberg *et al*, 2009). As a result, SMT potentially influences central mechanisms and motor responses that promote physical function, and potentially, sensory function and stability (Ageberg *et al*, 2009).

Observation studies have showed that muscle coordination and proprioception acuity is deficient even six months after TKR (Bascuas *et al*, 2013; Swinkels & Allain, 2013; Swinkels *et al*, 2009). A two month post-surgery period was considered sufficient to avoid pain and effusion exacerbation for the safe initiation of SMT (Fung *et al*, 2012; Liao *et al*, 2013; Piva *et al*, 2010), and to have provoked no adverse effects. Therefore, given the clinically important results by the studies by Liebs *et al* (2012), Piva *et al* (2010) and Liao *et al* (2013), it can be understood that the initiation of SMT within the first two months post-surgery, is acceptable and essential. Thus, any compensatory protective strategies in proprioceptive and gait control already learned and established in OA patients that had been associated with the pathway to TKR (Gauchard *et al*, 2010; Lytinen *et al*, 2010; Messier *et al*, 2000), would be eliminated. However, studies that had initiated programmes early (6th day, post-TKR) versus late (14th day) offered marginal patient-reported gains (WOMAC, medium effect size) (Gauchard *et al*, 2010; Liebs *et al*, 2012), thus allowing clinicians to initiate SMT even within the first week of rehabilitation. Interestingly, THR replacement patients showed that early versus late training can give opposite outcomes compared to TKR patients, suggesting surgery-specific mechanisms of recovery (Liebs *et al*, 2012). A non-RCT study by Gauchard *et al* (2010), investigating recovery of posturo-motor strategies post-TKR with SMT at two stages: firstly, after the elimination of pain and secondly, after a six week enhanced sensori-motor rehabilitation programme (started within a few days after TKR), also showed that postural regulation (posturography analysis) required approximately one month to reach that of age-matched controls. Thus, a safe time for clinicians to initiate SMT seems to be within two weeks following TKR.

Regarding the duration of the SMT, most of the studies reviewed had implemented 6 - 8 weeks' programmes of supervised exercise (>one session·week⁻¹; 45-90 minutes). Nevertheless, optimal frequency, time and progression of dosage remain elusive due to methodological heterogeneity. The intervention groups in all studies offered improved functional and balance outcomes compared to controls when functional rehabilitation had been augmented with sensori-motor conditioning. No study had incorporated an iso-volumetric comparison (between usual care and usual care enhanced with sensori-motor elements), hindering evaluation of any possible advantages by SMT. Dose-response effects may therefore have been implicated in any gains that had been observed.

It was notable that PROMs (e.g. LEFS, ABC-S, WOMAC) could not always detect the changes identified by objective functional and balance measures, such as the TUG Test and SLSB, known for their good clinimetric responsiveness and prognostic validity of falls-likelihood (Fung *et al*, 2012; Piva *et al*, 2010). Improving postural control and lowering falls-related injuries will reduce health-care costs. However, there is no available information on the costs associated with the inclusion of a sensori-motor training programme or the cost-effectiveness of exercise programmes aimed at preventing falls in TKR patients.

The points for discussion within this review were underpinned by evidence from RCTs offering Level Ia robustness (PEDro scale 5 - 7), sound methodologies, minimal patient' numbers that had been lost to follow-up.

Limitations

This review has identified only five studies of limited sample sizes investigating the addition of sensori-motor elements to physiotherapy regimes post-TKR surgery, as only a few studies have been published in this field. The study by Liebs *et al*, (2012), implemented balance exercises within a functional exercise programme implemented in a combination of aquatic and land-based environment. It can be understood that the impact of forces and stimuli on receptors implemented within a land-based and water-based environment induce different physiological and biomechanical responses (Kutzner *et al*, 2017), and therefore effects could not be directly comparable with those from the other included studies. However, it was thought important to include it within the systematic review as it was the only study at the time that had attempted to add SMT components earlier than two months post-surgery. The research question and inclusion criteria fulfilled the PICO components. An extensive review of the literature was performed, with more than two databases searched and studies' reference lists and did not deviate from the original protocol of study conduct. The inclusion of only English language studies might have introduced bias, while the exclusion of TKR studies involving patients with co-morbidities such as rheumatoid arthritis, limited the generalisation of findings. Therefore, this systematic review limited also by the small number of included studies offered some novel data on the effect of SMT and speculation on its optimal implementation.

The PEDro scoring suggested adequate robustness of methodological approaches in the studies that had been included. Nevertheless, the experimental design of most studies was underpowered and had shunned iso-volumetric comparisons, precluding robust interpretation of the contribution of balance and proprioception training, and also the generalisation of outcomes. The design of the studies had different outcomes and limited follow-up assessments. Eight is a suitable number of trials to draw conclusions; however, the subgroup analysis was based on fewer trials. Heterogeneity of outcome measures, timing of training initiation, and volume of exercise, precluded meta-analytical approaches for the synthesis of evidence. All studies in this review offered critical discussion of findings, description of potential clinical impact, and contextualisation within the contemporary literature. However, although the sample recruitment and selection was acceptable, generalisation of findings should be made with caution, and would only be feasible in patients with knee OA undergoing primary TKR.

Suggestions for future research

Firstly, a more robust adequately powered RCT should be conducted on providing vital data, on the effects of SMT, not as an additional element extending the duration of the exercise programme, but within an equivalent duration exercise programme, in the functional mobility and sensori-motor function of OA patients undergoing TKR. Secondly, the type and dosage components of exercise should be investigated and incidence of falls should be also considered as a measurement outcome.

A future systematic review should incorporate RCTs implemented in land based-environments post-operatively. Dose-response effects should be monitored in a potential meta-analysis for more concrete findings. Finally, the factors such as any symptoms, quality of life domains, functional or sensori-motor deficits as determinants of balance should be examined.

6.6 Conclusion

Overall, this systematic review provided robust evidence (IIa) (5-7 PEDro score) for the incorporation of SMT into the usual care involving functional training programmes. This approach offers an acceptable and targeted additional component within the interventions of patients following TKR for improving balance performance. Sensori-motor training implemented for 6 - 8 weeks and initiated two

weeks post-TKR, may be effective and tolerated well by patients, with no fear of adverse effects in physical function. However, a lack of acceptable effect size in some studies, combined with underpowered experimental designs, suggested the possibility of either a lack of potency of intervention or a compromised capability to detect subtle gains that might have been offered by the intervention. Both aspects threaten what might be generalised from the findings in this population. Optimal intensity and frequency of exercise during training, and criteria of progression warrant further investigation.

Chapter 7

Single-measurement reliability and reproducibility of indices of functional, sensori-motor, neuromuscular and musculoskeletal performance in a clinical population of patients undergoing TKR.

Abstract

Background and Purpose: The aim of this chapter was to evaluate the reproducibility and single-measurement reliability (ICC) of selected indices of functional, sensori-motor, neuromuscular and musculoskeletal performance that have been deployed within the main study of this thesis.

Methods: Fifty-two knee OA patients (13 male: age 70.2 ± 5.4 years; height 1.70 ± 0.06 m; body mass 88.3 ± 6.6 kg, 39 female: age 72.9 ± 5.5 years; height 1.63 ± 0.04 m; body mass 80.1 ± 9.6 kg) were selected from a consecutive series of patients electing TKR at University Hospital Rion. Indices of functional, neuromuscular, sensori-motor and musculoskeletal performance were examined for single measurement reliability, reproducibility, and stability at pre-surgery, at 8 weeks and 14 weeks post-surgery.

Results: Excellent single-measurement reliability were demonstrated for each of the outcome measures of functional (TUG: ICC > 0.98), neuromuscular (PF and EMG-derived indices [amplitude]: ICC > 0.98 and ICC > 0.84), sensori-motor (JPE: ICC > 0.70) and musculoskeletal (CSA of rectus femoris in contraction: ICC > 0.98) performance, with no qualitative differences amongst experimental conditions. Results were in accordance with the relevant literature. Measurement reproducibility as indicated by Bland & Altman limits of agreement for the TUG using repeated assessments, showed that there was no systematic bias between measurements and that any difference between the measurements was not related to the magnitude of the measured score.

Conclusions: The levels of measurement reproducibility (precision), and the concomitant capability to confidently assess changes in an individual patient's performance capability, suggested that the measurements associated with the non-operated limb were more reproducible than those for the limb undergoing surgery. Estimates of measurement precision based on the MDC of the primary outcome measure, TUG, showed that an individual patient's performance would need to change by more than $\pm 1.7s$ (95 % confidence limits) to confidently exceed error associated with a single assessment of TUG and to confirm 'real' performance gains or losses. However, whilst acceptable error variability and excellent measurement reproducibility was shown for the TUG Test, rectus femoris muscle' CSA and

quadriceps muscle strength (PF), moderate to high reproducibility levels (ICC: 0.60 - 0.83) and large variability (coefficient of variability >10 %) was recorded for measures of proprioception (JPE). Overall, it was concluded that the selected outcomes offered competent levels of reproducibility and single-measurement reliability characteristics for both operated and non-operated limbs to be used within the main study of the thesis (Chapter 8).

7.1 Introduction

The purpose of this chapter was to assess the single-measurement reliability and reproducibility of selected indices of functional, sensori-motor, neuromuscular and musculoskeletal performance in a clinical population of patients undergoing TKR. This study of reproducibility and single-measurement reliability together with the clinimetrically-focused review of the literature (Chapter 3) offers important evidence to clinicians and researchers about the limits to the quality of measurement that might be used to underpin the selection of the components of rehabilitative training. This information about the quantity of error or precision inherent in each candidate outcome measure and corresponding confidence in detecting particular sizes of performance changes in patients was helpful in contextualising each outcome's utility within a group-based experimental design, such as that in the main study (Chapter 8). Table 7.1 presents a summary of candidate outcome measures, some of which are relatively novel within the literature of TKR clinical population (e.g. force error, peak force and rectus femoris' CSA), and some which have been used regularly in TKR literature, and which ultimately had been selected for use in this thesis.

Therefore, the aim of this chapter was to assess the single-measurement reliability and reproducibility of selected indices of functional, sensori-motor, neuromuscular and musculoskeletal performance in a clinical population of patients undergoing TKR. The rationale for the current study was to establish the estimates of reliability measurement error and stability for outcome measures selected for the main RCT of the thesis. The researcher (MM) had been familiarised with the dynamometer and real time ultrasound within her clinical practice for over five years. However, the researcher had received training within the QMU on the use of ultrasound for rectus femoris specifically, as well as on the use of the EMG equipment and analysis from researchers with over 20 years of experience. Therefore, it was considered important to assess intra-rater reliability. The study's findings would allow contextualisation of the selection of indices of performance (outcomes) that were to be used in the main data chapter of the thesis (Chapter 8), and offer an appreciation of the clinimetric limitations associated with using such outcomes to describe changes in the performance capabilities of individual patients.

Table 7.1 Summary of the clinimetric qualities of novel outcome measures, and those most regularly used in TKR rehabilitation selected in the main study.

Name	Type of outcome measure	Main construct being measured	Clinimetric properties
TUG	Objective	Mobility and balance	ICC = 0.97; SEM = 1.07 s; MDC = 2.49 s, defined in OA patients. (Kennedy <i>et al</i> , 2005)
Postural stability (BSS force platform)	Objective	Balance	ICC > 0.87; MDC ≈ 3°, defined in healthy participants (Perreira <i>et al</i> , 2008)
JPE (active or passive repositioning method)	Objective	Sensori-motor performance	ICC > 0.70; SEM of 2.3° defined in healthy participants. (Knoop <i>et al</i> , 2011)
PF	Objective	Neuromuscular performance	ICC = 0.98; MDC = 25.02 N, defined in OA patients. (Kean <i>et al</i> 2010)
Visual Numeric Pain Rating Scale	PROM	Pain	ICC = 0.96; MDC = 2 cm defined in OA patients. (Farrar <i>et al</i> , 2001)
KOOS; KOS-ADL	PROM	Mobility and function	ICC > 0.74 and ICC = 0.97, respectively; MDC = 8 units; MDC = 12.5 - 17.2 units, respectively, defined in OA patients undergoing TKR. (Moutzouri <i>et al</i> , 2015; Irrgang <i>et al</i> , 1998)

TUG: Timed Up and Go; JPE: joint position error; PROM: patient-reported outcome measure; PF: Peak force; KOOS: Knee Injury Osteoarthritis Outcome Score; KOS-ADL: Knee Outcome Scale-Activities of Daily Living; ICC: Intraclass Correlation Coefficient; MDC: Minimal detectable change.

Contemporary empirical research and evidence-based clinical practice is often concerned with exploring changes in performance abilities associated with both intra-session (i.e. in comparisons of the performance capabilities of ipsilateral and contralateral limbs) and inter-day assessments (i.e. in the examination of the extent and rate of change of performance capability over time) (Eston & Reilly, 2009). A fundamental characteristic of any tool of performance capacity must be that it offers at least a minimal level of measurement precision commensurate with its intended purpose (Mercer & Gleeson, 2002). Clinicians need to be confident that any changes that are detected for an individual patient using a particular outcome are actually true changes that can be attributed to a clinical intervention being used. The

research investigations of reproducibility and measurement precision characteristics of outcomes can help to elucidate the limits of measurement utility in identifying true changes in performance, and thus, facilitate optimised clinical care. With regards to reproducibility of measurement, there are two necessary assumptions. The first is that a true score does not change between measurements. The second is that the period of time between measurements is long enough to prevent learning, carry-over effects, or recall.

The ICCs quantify the single-measurement reliability and the confidence with which measurements resemble each other in terms of a quantitative trait (McGraw & Wong, 1996). One of the distinctive characteristics of an ICC is its ability to examine more than two measures simultaneously (Shrout & Fleiss, 1979).

Standard error of the measurement (SEM) used for the evaluating absolute reliability of a measure. It is useful for providing a simple measure of the variability of actual scores and thus ultimately, an assessment of a measurement's quality (McManus, 2012). In other words, it estimates how repeated measures of a person's performance, on the same instrument, tend to be distributed around his or her "true" score. One of the limitations related to the expressing reliability in terms of SEM is that the true scores of measures are often unknown and no measurement can be constructed that provides a perfect reflection of it. Generally, a larger SEM represents the inferior consistency of an outcome measure. Since all measurements are prone to some errors, it is highly unlikely that exactly the same findings will be yielded even after repeating a test using exactly the same measuring tools and following exactly the same protocol designed for the test. An important distinction between the SEM and ICC is that the latter index of reliability, due to the nature of how each is calculated, is particularly influenced by the extent of the target population's variability (i.e. its homogeneity or heterogeneity, as indicated by smaller or larger standard deviations, and assuming that the sample is distributed normally).

While the SEM estimates the standard error associated with a set of repeated scores, the minimal detectable change (MDC) reflects the smallest score that is beyond the measurement error of an outcome measure. Therefore, it is likely to be helpful in representing the limits (expressed using relevant statistical confidence limits) between which the person's 'true' score might lie, and thus in identifying any

'real' changes in an individual patient's performance capability. Both are meaningful for clinical practice, as they are presented in the unit of the outcome measure and the MDC can be derived from the SEM (Stratford, 2004).

It had been reported in the literature that coefficient of variation (usually expressed as a percentage) (CV %) is one of the easiest calculation-based methods for computing the variability (reproducibility or precision) for any measurement across any number of trials (Shechtman, 1999). The actual value of the CV % is independent of the original unit, and thus dimensionless.

Bland & Altman plots (1983) have also been used in order to describe agreement and reproducibility between two quantitative measurements, by constructing limits of agreement. These statistical limits are calculated by using the mean and the SD of the differences between two measurements. To check the assumptions of normality of differences and other characteristics, a graphical approach is used. Horizontal lines are drawn at the mean difference associated with two repeated assessments, and at the limits of agreement, which are defined as the mean difference plus and minus 1.96 times the standard deviation of the differences. The latter represent 95 % confidence limits within which the 'true' differences between the repeated assessments might be expected to reside. Bland and Altman plots of this type are useful for revealing systematic biases and outliers (Giavarina, 2015).

When assessing measurements over time, with an intervention being applied, it is considered important to evaluate stability of measurements. Stability is an aspect of reliability and many researchers report that a highly reliable test indicates that the test is stable over time. Stability refers to the tendency for the underlying variable to be unchanged over time (Allen, 1981). Stability is important for assessment of measurement quality for two reasons. If one uses a test-retest association to estimate measure reliability, then one needs to be able to assess stability of the underlying measure. The obtained test-retest correlation coefficient reflects at least two sources of influence: random error in the measurement and a real change of the behavior over time. The first reflects the reliability of the measurement instrument, whereas the second taps the stability of the underlying behavior (Wiley & Wiley, 1970).

In the current study, with responses to a surgery procedure and a physiotherapeutic intervention being applied to patients, it would be important for clinicians and researchers to know the single-measurement reliability, reproducibility, measurement precision, as well as the stability of measures.

7.2 Methods

7.2.1 Participants

Fifty-two adults (13 male: age 70.2 ± 5.4 years; height 1.70 ± 0.06 m; body mass 88.3 ± 6.6 kg, 39 female: age 72.9 ± 5.5 years; height 1.63 ± 0.04 m; body mass 80.1 ± 9.6 kg) were selected from a consecutive series of patients electing TKR at University Hospital Rion (Greece, National Health Service). Consecutive patients (May 2012 - May 2014) undergoing primary standardised cemented TKR (single surgeon; 15-years' experience of knee replacement; 50 knee replacements per annum) were invited to participate in the study and were screened for study eligibility (ambulatory; clinical and radiological findings of advanced osteoarthritis; primary total knee replacement). After a complete description of the study, written informed consent was obtained from all patients. The study has been approved ethically by institutional Committees (University Hospital of Patras; Queen Margaret University Edinburgh, UK [7052/4-7-2011]).

7.2.2 Study Protocol

Baseline measurements for all outcome measures were taken at pre-surgery (0 weeks), along with basic demographic data and any relevant concomitant medical history. At assessment sessions two and three (8 and 14 weeks post-TKR), the outcome measures were repeated. For a period of two weeks post-surgery, standardised care was provided to all participants. Subsequently for a 12-weeks period (2nd week to the 14th week), two time-matched rehabilitation programmes were undertaken for the two groups of participants. Please see main thesis' study (Chapter 8, pages 227- 231) for a detailed schedule of its experimental design, from which this data have been derived.

Every effort was made to assess the outcome measures at the same time of day within each patient's schedule of assessment sessions, in order to minimise the intrusion of error associated with circadian variation. The order of the measurements was randomly assigned for each patient, at all assessment sessions. All participants

undertook a warm-up programme before testing, with patients choosing between 5-10 minutes of static cycling or an equivalent period of walking and following this with five minutes of static stretching of the involved musculature.

Within each assessment session, scores from three trials for each outcome of functional (Timed Up and Go Test-TUG) (Kennedy *et al*, 2005), sensori-motor (joint position error-JPE) (Olsson *et al*, 2004; Gleeson *et al*, 2013; Peer *et al*, 2016), and neuromuscular performance (peak force-PF, Peak amplitude-Peak Amp.). (Gleeson *et al*, 1996; Minshull *et al*, 2009) were obtained from all patients, as the protocols described and tested for reliability elsewhere in the literature. Scores from two trials for the outcome of musculoskeletal performance (Cross sectional area of rectus femoris muscle-CSA_{RF}) were obtained, as the protocol described and tested for reliability in the relevant literature (Bembem, 2002; Noorkoiv *et al*, 2010).

7.2.3 Outcome measures

The description of the measurement procedure of the battery of selected indices used within the main study of the thesis (Chapter 8) is presented in this section.

7.2.3.1 Functional mobility

Timed Up and Go (TUG) Test

The TUG is a test of the manoeuvres required for functional mobility (Podsiadlo & Richardson, 1991). The test involves patients rising from a chair with armrests, walking 3 m, turning, and walking back to sit down. The task was performed at a well-tolerated, self-paced speed by the subject. The stop watch was started on the “go” and stopped as the patient sat down. At all three assessment sessions (0 weeks, 8 weeks and 14 weeks). Participants undertook the TUG three times, with at least a minutes rest between each time. The first occasion was to familiarise them with what was required. The second and third occasions were recorded as the test time and the mean was of the second and third was used for analysis.

7.2.3.2 Sensori-motor performance

For the assessment of sensori-motor performance, joint position error was selected. For this purpose, a dynamometer (Primus RS, dynamometer) was used in order to examine patients' ability to actively reposition their knee in selected angles (25 and 60 degrees (°) of knee flexion). The protocol followed, as described below, has been

often used in the literature previously (Olsson *et al*, 2004; Gleeson *et al*, 2013; Peer *et al*, 2016). In the sitting position, participants were seated with back support and the hip at an angle of 80 ° of flexion. A baseline bubble inclinometer was attached on a soft Velcro cuff on each shin with double-sided adhesive tape. Reproduction of knee angles was performed in open kinetic chain manner. From a reference angle (full knee extension, 0 °), the investigator from a full extended position moved the leg to the target angle position and was held there for 5s to allow patient to memorize the position. After a 5s interval, the patient was required to move the involved lower extremity actively from a fully extended position to the specific angle and then return it to the reference angle with eyes closed in five discrete trials. The patient acknowledged verbally when they believed that they had achieved the target angle. Patients were placed in a seated position on the dynamometer with the leg to be assessed for sensori-motor performance moving actively toward a designated target angle of joint flexion. The lower leg was supported at a position 10 - 15 cm proximal to the lateral malleolus by an adjustable rigid system. Two target angles were set.

Three attempts were recorded for patients trying to match 25 ° and another three attempts for 60 ° of knee flexion. The mean JPE score across the three trials was used for the subsequent data analysis. Joint position error was recorded as the mean angular discrepancy from the target during three replicates at each of the two target knee angles, performed in random order (six trials, 15s inter-trial recovery), using the following expression (absolute values of estimated errors were used for analysis):

$$\text{Joint Position Error} = (\text{trial knee angle} - \text{target knee angle}) / \text{target knee angle} \times 100 \%$$

7.2.3.3 Neuromuscular performance indices

Peak Force (PF)

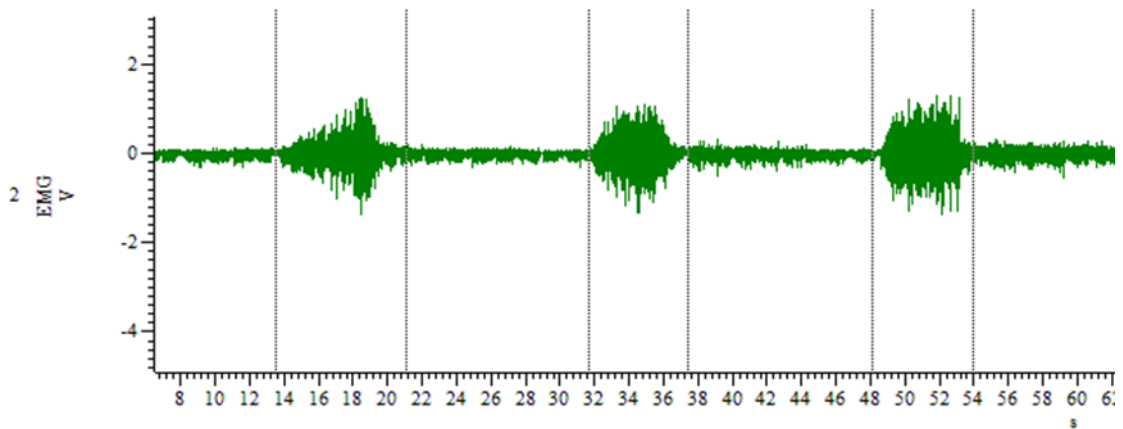
To test the knee extensors' PF, measured in Newtons, a dynamometer (Primus RS BTE Dynamometer, The Technology of Human Performance, USA) was used. Patients were secured in a seated position on the dynamometer with the hip flexion fixed to 90 degrees and the knee angle set at 60 ° of flexion. The lever-arm of the dynamometer was attached to the participants' leg via a padded ankle cuff and

adjustable strapping just proximal to the lateral malleolus. Further strapping was placed across the mid thoracic spine, pelvis and just above the anterior surface of the knee. The axes of rotation of the dynamometer and the knee joint were aligned as closely as possible. Following a series of sub-maximal warm-up muscle activations, a signal within 1 - 4s was given by the primary investigator to the participants for them to extend the knee as forcefully and rapidly as possible isometrically against the immovable restraint offered by the apparatus. Another cue was given to the participants after 2 - 3s of maximum voluntary isometric contraction (MVIC) to cue neuromuscular relaxation. Each MVIC was separated from the next by at least 10s (Gleeson *et al*, 1996; Minshull *et al*, 2009). Volitional maximal peak force was recorded as the greatest response from each of the three intra-session replicates of maximal isometric muscle activations of the knee extensors musculature. The mean PF score across the three trials was used for the subsequent data analysis.

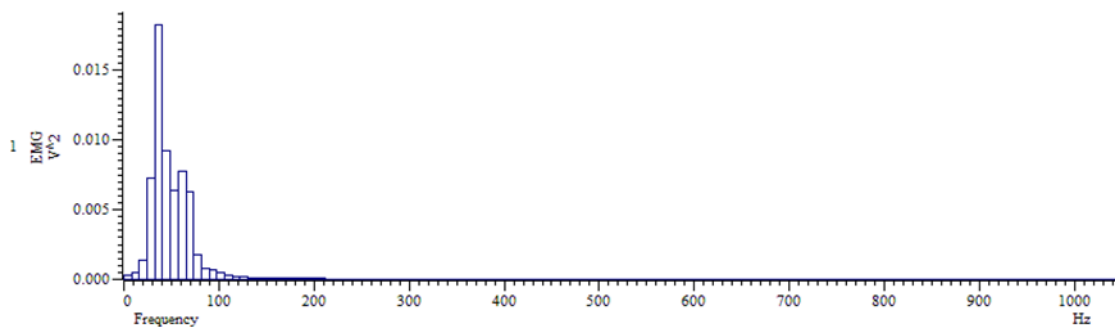
The assessment of neuromuscular performance was also indirectly measured for the quadriceps muscle by using electromyography (EMG) equipment. Raw unfiltered EMG signals were passed through a differential amplifier (impedance 10 M Ω , CMMR 100 dB, gain 1000; Cambridge Electronic Design, UK), analogue to digitally converted at 2.5 kHz sample rate (18), and remained unfiltered during subsequent analyses. It is well known that during isometric contractions, force and EMG amplitude are well correlated (Basmajian, 1974). Electromyography (EMG) is generated by a record of the electrical discharges of active motor units during muscle activation, and the root mean square (RMS) magnitude of EMG is commonly used to describe the time-domain information of the EMG signal (Guo *et al*, 2010). Commercially available software (Spike 2 software, version 5.16, Cambridge Electronics Design Ltd., UK) was used for all volitional data capture and interpretation. Figure 7.1 illustrates an example of EMG activity during three quadriceps isometric contractions and a relevant power spectrum analysis image.

Figure 7.1 a) EMG activity of isometric contraction of the rectus femoris in 60 degrees of knee flexion (Root mean square and peak amplitude were analysed); b) Power spectrum frequency analysis.

a)



b)



The EMG activity from the rectus femoris (RF) was recorded concomitantly with participants' performance of static peak force. The EMG was recorded using bipolar rectangular surface electrodes (self-adhesive, Ag/AgCl; 10 mm diameter; Unilect, UK) (Eston *et al*, 2009) that were applied longitudinally over the belly of the RF, on the line between the anterior superior iliac spine to the superior border of the patella (at 50 % of the distance from the greater trochanter of the femur to the lateral knee joint space), parallel to the orientation of the muscle fibres. The inter-electrode distance was 20 mm (center to center) (Hermens *et al*, 2000). A reference electrode was placed over the medial shaft of the tibia approximately 6-8 cm below the inferior pole of the patella (Hermens *et al*, 2000; Pincivero *et al*, 2003). Standardised skin preparation techniques (shaving of hair, light-skin abrasion and cleaning with alcohol) preceded electrode' placement to yield an inter-electrode impedance of less than 5 k Ω . The RMS of the RF muscle was measured over a 50 ms time period, corresponding to maximal isometric knee extension. Peak electrical activity, RMS,

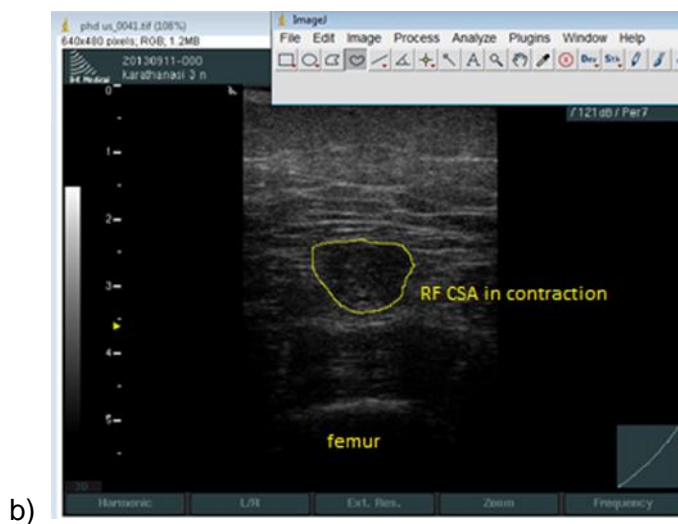
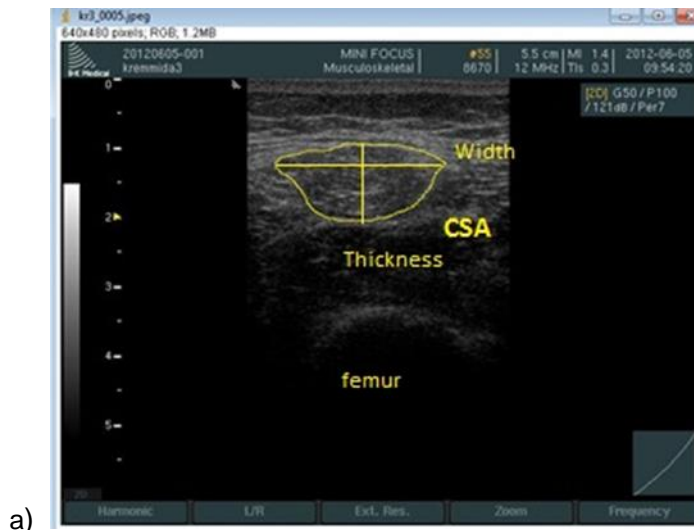
and frequency of muscle firing were used for the EMG data analysis. The RMS calculation is considered to provide the most insight on the amplitude of the EMG signal, since it gives a measure of the power of the signal, while producing a derived waveform that is easily analysed.

7.2.3.4 Assessment of muscle architecture

For the muscle architecture parameters, real time ultrasound BK mini focus, 7.1 MHz with a 55 mm linear probe was used. The probe was placed ventral to the transverse plane and perpendicular to the skin over the RF muscle. Rectus femoris was marked 3/5 from the distance of the anterior superior iliac spine to the superior border of the patella (Seymour *et al*, 2009). This was the highest point in the thigh that the entire rectus femoris cross-section could be visualised in a single field in all patients. Imaging was conducted in a seated position with the knee in 60 ° of flexion. Scanning depth was set to where the femur could be discerned for orientation. Gentle contraction-relaxation manoeuvres were employed to delineate muscle septa prior to image acquisition. The cross sectional area, muscle' thickness and width were taken at this point of the muscle.

Two images were captured with the muscle in maximum relaxation, and subsequently, another two images with the muscle during maximum voluntary isometric contraction (at the end of a 5s contraction). These images were 'frozen' and stored for further analysis. Analysis of images was performed with 'Image J' software (<https://imagej.nih.gov/ij/>). Special care was taken to avoid pressure with the probe on the patient's tissue during testing. The cross-sectional diameter of the RF is the distance between the fascia of the muscle (Figure 7.2).

Figure 7.2 Rectus femoris in relaxation (a) and contraction (b) in 60 ° for knee flexion during an isometric extension trial.



7.3 Statistical Analysis

Normal distribution of the data collected was assessed using the Shapiro Wilks in order to determine whether the data was normally distributed. Systematic fatigue or learning effects for intra-session group mean data for each of three trials variability was compared using one-way ANOVA.

Single-measurement test-re-test reliability was calculated for each outcome measure using the ICC (model 2,1) (Shrout and Fleiss, 1979). This two way ANOVA model was used because each of the participants was rated by a single

assessor (or measurement system) and the results were to be generalised to other raters.

For single-measurement test-re-test reliability purposes, the typical formula for ICC was obtained by dividing the true variance by the total variance as defined in the following expression:

$$ICC = (MS \text{ error between subjects} - MS \text{ error within-subjects}) / (MS \text{ error between-subjects} + ((k-1) * MS \text{ error within-subjects}))$$

(MS = mean square; k = number of measurements) (Strimpakos *et al*, 2005).

Coefficient of variation (CV %), corrected for small sample bias (Sokal and Rohlf, 1981), was used to compute variability of the indices across the two or three intra-session trials for each intra-session. The lower percentage scores represent less measurement variability and better reproducibility. Coefficient of variation was calculated according to the expression:

$$CV \% = (Standard \ Deviation / Mean) * (1 + [1/4n]) * 100, \text{ expressed as a percentage, where } n \text{ is the number of trials.}$$

Assessment of stability of measures over time could be reflected by performing an ANOVA on the CV % over time (i.e. increase/decrease over time) of the selected outcomes.

Standard error of measurement (SEM) was calculated using a mathematical expression involving both the sample population's SD and the computed ICC, as follows:

$$Standard \ error \ of \ measurement = SD * \sqrt{(1 - ICC)}.$$

While the SEM estimates the standard error in a set of repeated scores, as alluded to previously, the MDC relates to the smallest score that is beyond the limits of measurement error of an outcome and therefore, likely to contain a person's "true" score to within a certain level of confidence (often specified as $\pm 68\%$ and $\pm 95\%$ confidence limits). Both are meaningful for clinical practice, as they are presented in

the measurement unit of the outcome measure. The MDC can be derived from the SEM (Stratford, 2004), represented by the following formula:

$$\text{MDC}_{95\% \text{ CI}} = 1.96 * \sqrt{2} * \text{SEM},$$

where the 1.96 derives from the choice to offer 95% confidence for this estimate of error variance, and the multiplier of $\sqrt{2}$ is to account for the additional uncertainty introduced by using difference scores from measurements at two points in time (Haley & Fragala-Pinkham, 2006; Beckerman *et al*, 2001).

Limits of agreement were visualised using a Bland & Altman plot (Bland & Altman, 1986) for the selected outcome measures of TUG and CSA. The latter have been offered as novel examples of the type of analysis that could have been used for all of the indices within this study of measurement reproducibility. All data was analysed using SPSS version 16.0. In order to identify the intrusion of any systematic learning effects across trials within each testing occasion (intra-session), two-way (involving factors of assessment time (pre-surgery; 8 weeks post-surgery; 14 weeks post-surgery) and limb) repeated measure analysis of variance (ANOVA) was undertaken to test the null hypothesis of no differences amongst the group mean scores for serial intra-session trials for each outcome of interest.

7.4 Results

A detailed description of the data used in this study for each of the selected outcome measures, and providing data for each of the three intra-session trials that had been recorded, at each of the main study's three assessment occasions, can be found in Table 7.2. Summary descriptive statistics (means and SD values) for the selected outcomes are presented in Table 7.3.

Normal distribution of the data was confirmed using Shapiro Wilk's tests (Table 7.4) with very few variables showing statistically significant values.

Most of the outcomes showed no systematic carry-over (fatigue or learning) effects when intra-session group mean data for each of the three trials variability was compared using ANOVA ($p > 0.05$). A carry-over effect amongst the three trials was noted only for the PF ($F_{(1.6,83.0)GG} = 5.8$; $p < 0.05$) at baseline and the JPE_{25°}

($F_{(1.8,78.5)GG} = 24.1; p < 0.01$) and JPE_{60° ($F_{(1.6,81.2)GG} = 10.1; p < 0.01$) of the operated limb at the 8-weeks session. Post-hoc Bonferroni corrections were used to identify which trial amongst the three was statistically significant, and therefore excluded from subsequent analysis. These findings suggest that intra-session changes in the selected outcomes can be attributed to the random technical or biological variation associated with the effects of the patient interacting with the equipment used for assessment.

Table 7.2. Descriptive data (means and standard deviations) for each of the three intra-session trials that were recorded for selected outcome measures, at each of the three assessment occasions.

TUG:

Outcome measures	Assessment Occasion 1			Assesment Occassion 2			Asesment Occasion 3			Sig.
	Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3	
TUG (s)	16.3 (3.6)	16.4 (3.8)	N/A	13.1 (4.1)	13.2 (3.8)	N/A	10.1 (3.0)	10.3 (3.1)	N/A	ns
JPE_{25 op.} (%)	28.2 (17.9)	33.5 (17.4)	35.2(17.6)	23.4 (16.1)	22.7(13.6))	26.2 (17.3)	9.4 (15.4)	20.7 (18.1)	¹ 23.8 (18.7) ²	ns
JPE_{25 non-op.} (%)	27.5(18.2)	27.5 (17.6)	27.5 (17.1)	24.5 (12.6)	26.5 (14.1)	24.5 (12.6)	21.7 (14.4)	23.8 (13.0))	25.3 (16.8)	ns
JPE_{60 op.} (%)	17.5 (9.6)	(17.8 (9.5)	19.4 (9.3)	9.5 (7.8)	10.6 (8.3)	11.0 (7.0)	5.2 (8.4)	10.1 (7.9)	9.6 (8.2) ³	ns
JPE_{60 non-op.} (%)	13.5 (8.4)	14.2 (7.0)	16.7 (8.7)	10.5 (7.3)	10.3 (7.1)	11.0 (7.0)	9.6 (7.5)	9.5 (5.9)	9.5 (6.3)	ns
PF_{op.} (N)	39.8 (16.3)	41.7 (17.1)	43.0 (18.3) ⁴	46.9 (16.3)	47.4 (18.4)	49.0 (19.1)	60.8 (21.3)	61.5 (21.9)	62.4 (21.0)	ns
PF_{non-op.} (N)	55.0 (18.1)	55.5 (19.6)	56.5 (19.9)	61.1 (23.0)	61.3 (22.8)	63.0 (21.6)	73.1 (22.8)	73.5 (23.0)	75.1 (23.3)	ns
Peak Amp_{op.} (mV)	0.5 (0.2)	0.6 (0.3)	0.5 (0.2)	0.7 (0.3)	0.8 (0.2)	0.8 (0.3)	1.2 (0.7)	1.2 (0.6)	1.3 (0.7)	ns
Peak Amp_{non-op.} (mV)	0.6 (0.2)	0.7 (0.3)	0.7 (0.3)	0.8 (0.3)	0.8 (0.2)	0.7 (0.3)	0.9 (0.3)	0.9 (0.2)	0.9 (0.3)	ns
CSA_{rel.op.} (mm²)	435.1(71.6)	436.8 (70.4)	N/A	524.8 (80.3)	528.3 (78.6)	N/A	636.1 (125.2)	639.1(125.0)	N/A	ns
CSA_{rel.non-op.} (mm²)	473.4 (68.1)	473.4 (68.5)	N/A	554.2 (79.3)	558.3 (78.5)	N/A	638.8. (90.2)	638.2 (89.8)	N/A	ns
CSA_{contr.op.} (mm²)	341.5 (67.8)	340.9 (67.1)	N/A	447.5(85.5)	447.4 (86.8)	N/A	546.0 (121.3)	545.8 (122.0)	N/A	ns
CSA_{contr. non-op.} (mm²)	386.3 (68.6)	386.7(65.3)	N/A	486.3(82.2)	485.8(82.6)	N/A	563.8 (88.7)	563.2 (88.1)	N/A	ns

Timed Up and Go; JPE: Joint position error; PF: Peak Force; Peak Amp. : EMG Peak Amplitude CSA_{RF}: Cross sectional area Rectus femoris;

¹ A carry-over effect was noted between trial 1 and the means of trial 2 and 3 ($F_{1.6;78.5} = 24.1$; $p < 0.01$), and therefore for subsequent analysis trial 2 and 3 were used.

²A carry-over effect was noted between trial 3 and the means of trial 1 and 2 ($F_{1.6;83.0} = 5.8$; $p < 0.05$), and therefore for subsequent analysis trial 1 and 2 were used

³A carry-over effect was noted between trial 1 and the means of trial 2 and 3 ($F_{1.6;81.3} = 10.8$; $p < 0.01$), and therefore for subsequent analysis trial 2 and 3 were used.

Table 7.3 Summary descriptive statistics of selected outcomes (Mean (SD)).

Outcome Measures (units)	Assessment Occasion 1 (pre-surgery)	Assessment Occasion 2 (8 weeks post-surgery)	Assessment Occasion 3 (14 weeks post-surgery)
TUG (s)	16.4(3.7)	13.1 (3.9)	10.2 (3.1)
OSI _{op.} (°)	4.0 (1.4)	1.5 (1.3)	2.6 (1.2)
OSI _{non-op.} (°)	3.3 (1.7)	2.8 (1.2)	2.4 (1.1)
JPE _{25° op.} (%)	32.3 (14.9)	24.1 (13.4)	22.3 (17.6)
JPE _{25°non-op.} (%)	27.5 (15.3)	5.2 (10.6)	23.6 (12.8)
JPE _{60° op.} (%)	18.2 (8.6)	10.4 (7.1)	9.5 (7.5)
JPE _{60°non-op.} (%)	14.8 (7.1)	10.6 (6.0)	9.6 (5.1)
PF _{op.} (N)	40.7(17.0)	47.9(18.1)	61.6 (21.3)
PF _{non-op.} (N)	56.2(18.5)	62.4 (22.0)	73.9(23.0)
Peak Amp _{op.} (mV)	0.6 (0.2)	0.8 (0.4)	1.2(0.7)
Peak Amp _{non-op.} (mV)	0.6 (0.2)	0.8 (0.2)	0.9 (0.2)
CSA _{CONTR. op.} (mm ²)	341.2 (67.8)	447.5(86.6)	545.9(121.5)
CSA _{CONTR. non-op.} (mm ²)	386.5 (67.2)	487.6 (82.3)	563.5(88.3)

TUG: Timed Up and Go; OSI: Overall Stability Index; JPE: Joint position error; Op.: operated; PF: Peak Force; Peak Amp.: Peak Amplitude; CSA: Cross-sectional area; Contr.: Contracted.

Table 7.4 Assessment of data normality at baseline, 8 weeks and 14 weeks.

Normality Shapiro-Wilk Sig (2-tailed)	Age	weight	Baseline					8 weeks					14 weeks				
			TUG	JPE	PF _{OP}	Peak Amp.	CSA _{RF}	TUG	JPE	PF	Peak Amp.	CSA _{RF}	TUG	JPE	PF	Peak Amp.	CSA _{RF}
FET	0.06	0.48	0.99	0.86	0.10	0.06	0.36	0.07	0.22	0.15	0.04*	0.32	0.35	0.92	0.04	0.06	0.65
ESMET	0.16	0.09	0.16	0.87	0.85	0.01*	0.21	0.82	0.32	0.28	0.67	0.73	0.14	0.03*	0.51	0.15	0.001**

ESMET: Enhanced sensori-motor exercise training; FET: Functional exercise training; TUG: Timed Up and Go; JPE: Joint position error; PF: Peak Force; Peak Amp.: Peak Amplitude; CSA_{RF} : Cross sectional area Rectus femoris; * $p < 0.05$; ** $p < 0.01$

The findings describing the extent of random variability, reproducibility and single-measurement reliability are shown in Table 7.5 and Table 7.6.

Reliability of TUG Test

Results for the TUG Test had shown excellent single-measurement reliability at all three testing occasions ($ICC_{(2,1)}$: 0.99, 0.98, and 0.99 at pre-surgery, and at 8 weeks and 14 weeks following TKR, respectively; Table 7.5). Coefficient of variation has shown scores that progressively increased from pre-surgery assessment occasion (26.4 %) to 14 weeks post-surgery (35.5 %) (Table 7.6). Moreover, CV % for TUG Test before surgery was significantly lower compared to after surgery ($F_{(1.7, 89.6)GG} = 9.1$; $p < 0.001$), indicating change of stability of measurements over time. As it can be seen from the Bland & Altman limits of agreement plots (Figure 7.1a, b, c), the deviation of the mean from zero was minimal ($< 0.2s$) at all assessment occasions for the TUG outcome. The 95 % limits suggest that a performance change above 1.6s within the TUG would represent a “true” change, which is not merely due to measurement error. Results for MDC, using 95 % confidence limits (Table 7.6), showed similar patterns of measurement precision for TUG, with a ‘true’ change in performance for individuals within this population being indicated by scores altering by more than $\pm 1.7s$, for those patients scoring close to the group mean TUG score.

Reliability of JPE measurements for 25° and 60° of knee flexion

Joint position error measurements had achieved moderate to good reliability ($ICC_{(2,1)}$: 0.60 -0.83) and clinically acceptable SEM (%) scores (4.0 % - 9.3 %; i.e. 2° - 9 °); at 68 % confidence levels) during all three testing occasions for both operated and non-operated limbs and for both target angles (25° and 60°) (Table 7.5). The MDC (%) was found as 25.8 % at JPE_{25° and 11.0 % at JPE_{60° , showing that a ‘real’ change in sensori-motor performance would be confirmed above this value. However, coefficient of variation has shown large measurement errors and low precision (30.8 % to 84.2 %), across the assessment occasions for both limbs (Table 7.6). Moreover, CV % for JPE_{25° did not show equivalent levels before surgery and after surgery, for the operated limb ($F_{(1.6, 83.3)GG} = 6.0$; $p < 0.001$). More specifically, CV % for JPE_{60° was lower before surgery compared to after surgery, and was also lower for the non-operated limb compared to the operated limb ($F_{(1.0, 0.9)GG} = 12.6$; $p < 0.001$). Given that the raw ES for group mean JPE scores during the period of surgery and rehabilitation was < 10.0 % (Table 7.4), then both MDC and CV % might

suggest that for individual patients, relatively large measured changes in performance would be needed to confer confidence in the efficacy of an intervention (or indeed, de-conditioning if that was to occur, and there had been a concomitant reduction in sensori-motor performance).

Reliability of Peak Force during maximum voluntary isometric contraction for knee extensors

Peak force for the quadriceps muscle had achieved excellent single-measurement reliability ($ICC_{(2,1)} > 0.97$) during all three testing occasions, for both operated and non-operated limbs (Table 7.5). As shown by the measurement error' limits suggested for SEM (3.1 N) and the MDC (8.6 N), a performance score for an individual patient undergoing TKR that has changed by more than 8.6 N might be seen as a true change (with 95 % confidence limits) in performance that has exceeded the likely measurement error. However, coefficient of variation (68 % confidence limits) has shown relatively low variability for the assessment of peak force in patients undergoing TKR (~4.2 % – 12.0 %) (Table 7.6) with significantly lower levels presented after surgery ($F_{(1.8, 91.7)GG} = 28.6$; $p < 0.001$). No difference for the CV % was noted amongst limbs over time. Given that the raw ES for group mean peak force scores during the period of surgery and rehabilitation was < 20.2 N (Table 7.4), then both MDC and CV % might suggest that for individual patients, relatively small measured changes in performance would be needed to confer confidence in the efficacy of an intervention, or indeed, de-conditioning if that was to occur, and there had been a concomitant reduction in measured strength performance.

Reliability of EMG-derived indices [peak amplitude] for knee extensors

Peak amplitude for the quadriceps muscle is one of the indices included in the current study that had achieved a clinical acceptable ICC during all three testing occasions for both operated and non-operated limbs ($ICC_{(2,1)}$: operated vs. non-operated, 0.87 vs. 0.92, 0.88 vs. 0.84 and 0.96, vs. 0.87 at pre-surgery, 8 weeks and 14 weeks following TKR, respectively) (Table 7.5). As depicted by the SEM and MDC, a value above 0.3 mV would be taken as indicating a 'true' change in individual patients' neuromuscular performance. However, coefficient of variation has shown a large range of scores for this outcome (~24.0 % - 63.0 %) (Table 7.6). The CV % showed equivalent levels of measurement reproducibility for peak

amplitude at pre-surgery and post-surgery assessment occasions, as well as for both operated and non-operated limbs ($F_{(2,98)} = 0.2$; ns).

Reliability and reproducibility of the rectus femoris muscle' CSA during contraction

Results for the rectus femoris muscle' CSA had shown excellent reliability at all three testing occasions ($ICC_{(2,1)} > 0.98$) (Table 7.5). Coefficient of variation has shown acceptable variability (16.5 % -23.2 %) (Table 7.6). Moreover, CV % for CSA during contraction did not show significant difference amongst limbs over time, indicating stable measurements over time ($F_{(1.8,91.7)GG} = 0.4$; ns). Bland & Altman (Figure 7.2a,b,c,d,e,f, please refer to Appendix II) LoA scores suggested that a change in performance above 31.0 mm², and to a similar extent (> 35.6 mm²) as indicated by MDC scores, would be noted as a 'true' change in performance that is above the measurement error recorded for rectus femoris muscle' CSA scores in this population of patients undergoing TKR.

Table 7.5 Intraclass correlation coefficients (ICC), confidence intervals (95% CI) and standard error of measurement (SEM) for indices of functional, sensori-motor, neuromuscular and musculoskeletal performance at pre-surgery, and at 8 weeks and 14 weeks following TKR for the operated and non-operated limbs.

Outcome measures	Pre-surgery			8 weeks			14 weeks		
	ICC _{2,1}	95% CI	SEM	ICC _{2,1}	95% CI	SEM	ICC _{2,1}	95% CI	SEM
TUG (s)	0.99	0.98-0.99	0.4	0.98	0.98-0.99	0.6	0.98	0.97-0.99	0.4
JPE _{25°op.} (%)	0.68	0.53-0.71	8.4	0.69	0.54-0.70	7.4	0.83	0.72-0.90	7.2
JPE _{25°non-op.} (%)	0.63	0.59-0.75	9.3	0.60	0.50-0.67	6.7	0.63	0.48-0.75	7.8
JPE _{60°op.} (%)	0.76	0.65-0.84	4.2	0.69	0.56-0.79	4.0	0.73	0.57-0.83	3.9
JPE _{60°non-op.} (%)	0.67	0.54-0.78	4.1	0.69	0.50-0.69	3.5	0.70	0.55-0.83	2.8
PF _{op.} (N)	0.97	0.96-0.98	2.9	0.97	0.96-0.98	3.1	0.99	0.99-0.99	2.1
PF _{non-op.} (N)	0.97	0.95-0.98	3.2	0.98	0.97-0.99	3.1	0.99	0.99-0.99	2.3
Peak Amp _{op.} (mV)	0.87	0.79-0.92	0.1	0.88	0.81-0.93	0.1	0.96	0.93-0.97	0.1
Peak Amp _{non-op.} (mV)	0.92	0.88-0.96	0.1	0.84	0.75-0.90	0.1	0.87	0.80-0.92	0.1
CSArelax _{op.} (mm ²)	0.99	0.99-0.99	7.1	0.99	0.98-0.99	7.9	0.99	0.99-0.99	12.5
CSArelax _{non-op.} (mm ²)	0.99	0.99-0.99	6.8	0.99	0.99-0.99	7.8	0.99	0.99-0.99	8.9
CSAcontr _{op.} (mm ²)	0.99	0.99-0.99	6.7	0.99	0.99-0.99	8.6	0.99	0.99-0.99	12.2
CSAcontr _{non-op.} (mm ²)	0.98	0.97-0.99	6.6	0.98	0.97-0.99	11.6	0.99	0.99-0.99	8.8

CI: Confidence limits; Op.: operated; Non-op.: non-operated; TUG: Timed Up and Go Test; JPE: Joint position error; PF: peak force; Peak Amp: Peak amplitude; CSA: muscle Cross sectional area; relax: muscle in relaxation; contr.: muscle in contraction.

ICC ≥ 0.75 = excellent, ≥ 0.6 and < 0.75 = good, < 0.6 = fair.

Table 7.6 Coefficient of variation (CV %) for indices of functional, sensori-motor, neuromuscular and musculoskeletal performance at pre-surgery, and at 8 weeks and 14 weeks following TKR for the operated and non-operated limbs.

Variables	Pre-surgery		8 weeks		14 weeks		Sig.
	CV %		CV %		CV %		
TUG	26.4		34.8		35.5		0.001
	Operated	Non-op.	Operated	Non-op.	Operated	Non-op.	
JPE _{25°}	43.4	43.8	51.9	40.1	51.8	42.6	0.001
JPE _{60°}	30.8	84.2	55.9	49.3	53.0	42.9	0.001
PF	12.0	10.8	10.2	8.2	4.8	4.2	0.001
Peak Amp.	36.1	36.1	54.1	27.0	63.1	24.0	
CSA _{relax}	18.3	16.9	17.6	24.9	22.9	16.5	ns
CSA _{contr.}	23.2	20.3	22.6	19.7	22.2	19.3	ns

Non-op.: non-operated; TUG: Timed Up and Go test; JPE: Joint position error; PF: peak force; Peak Amp.: Peak amplitude; CSA: muscle Cross sectional area; relax: muscle in relaxation; contr.: muscle in contraction; sig: *p* value statistical significance of ANOVA investigation.

Analysis of variance on the CV % of the peak amplitude and CSA_{RF} has not shown statistically significant results, indicating stability of measurements of relevant indices over time (Table 7.6). However, ANOVA on the CV % of TUG, PF and JPE has shown statistically significant results. Therefore, after surgery and intervention was implemented, TUG and JPE have shown increased variability, whereas quadriceps PF showed decreased variability.

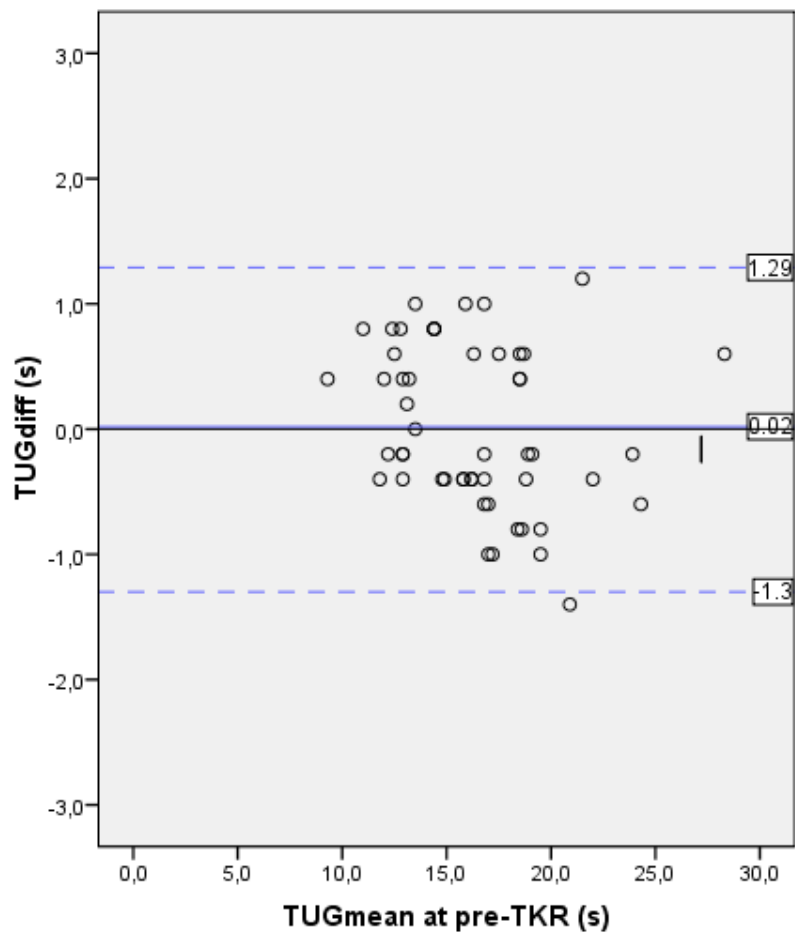
The Bland & Altman plots depicted below (Figure 7.1 and Figure 7.2) demonstrated good agreement between the two measurements recorded for the TUG Test and for the CSA of the rectus femoris at the three assessment occasions, since the majority of the data points had resided within the $\pm 95\%$ Limit, with very few outliers (Appendix II). As can be seen by the mean differences presented in Table 7.7, there is a deviation away from zero for measures related to CSA and for TUG at 14 weeks assessment session. This demonstrates a slight bias towards the first trial for the CSA_{RF} at the contracted state for both operated and non-operated legs. A bias towards the second trial was noted for TUG at the 14-week session.

Table 7.7 Mean difference between measurements (1st-2nd, intra-session), Limits of Agreement and MDC_{95%CI}.

Outcome Measure (units)	Mean difference (LoA)	Range of LoA 1.96 x SD diff	MDC _{95%CI}
TUG pre-surgery (s)	0.02 (-1.3 – 1.3)	2.6	1.1
TUG 8 weeks post-surgery (s)	0.03 (-1.6 – 1.6)	3.2	1.7
TUG 14 weeks post-surgery (s)	0.2 (-1.1 – 1.6)	2.7	1.1
RF CSA _{OP. CONTR.} pre-surgery (mm ²)	0.44 (-16.9 – 17.7)	34.6	18.6
RF CSA _{NON-OP. CONTR.} pre-surgery (mm ²)	0.32 (-31.3 – 30.8)	61.8	23.8
RF CSA _{OP. CONTR.} 8 weeks post-surgery (mm ²)	0.2 (-13.8 – 13.5)	27.3	33.7
RF CSA _{NON-OP. CONTR.} 8 weeks post-surgery (mm ²)	-0.54 (-21.3 – 21.9)	42.9	18.4
RF CSA _{OP. CONTR.} 14 weeks (mm ²)	-0.2 (-23.2 – 20.0)	43.2.0	32.1
RF CSA _{NON-OP. CONTR.} 14 weeks (mm ²)	-0.61 (-13.8 – 13.5)	26.6	24.4

TUG: Timed Up and Go; RF: rectus femoris muscle CSA: cross-sectional area; Op.: operated; LoA: limits of agreement; MDC: Minimum detectable change.

Figure 7.1a Bland & Altman plot for TUG Test pre-surgery (0 weeks).

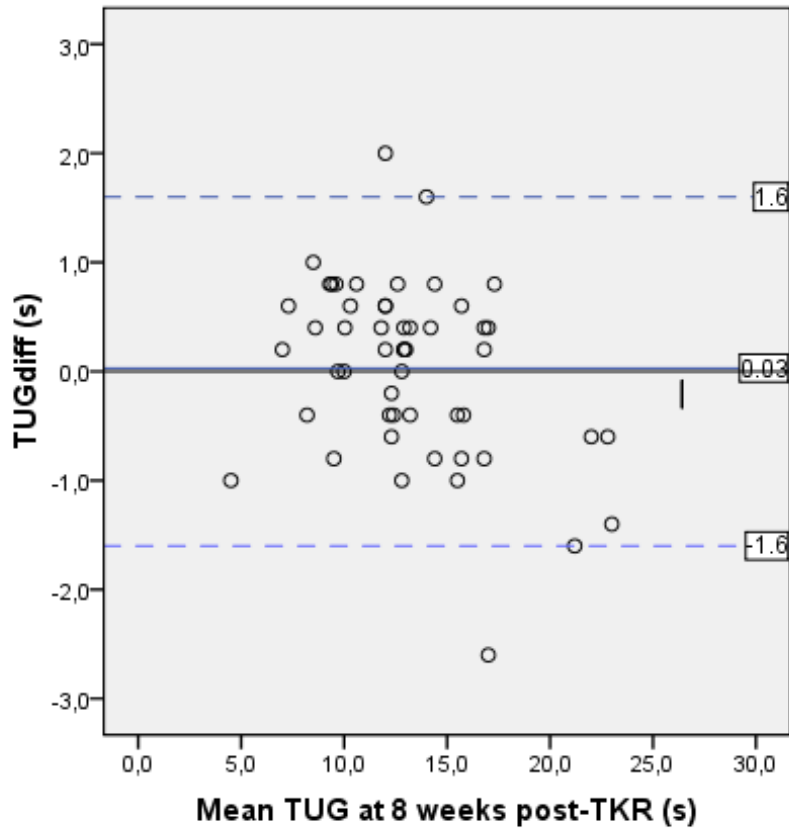


TUG: Timed Up and Go Test; diff: difference amongst trial measurements.

TUG: Timed Up and Go test; diff: difference amongst trial measurements.

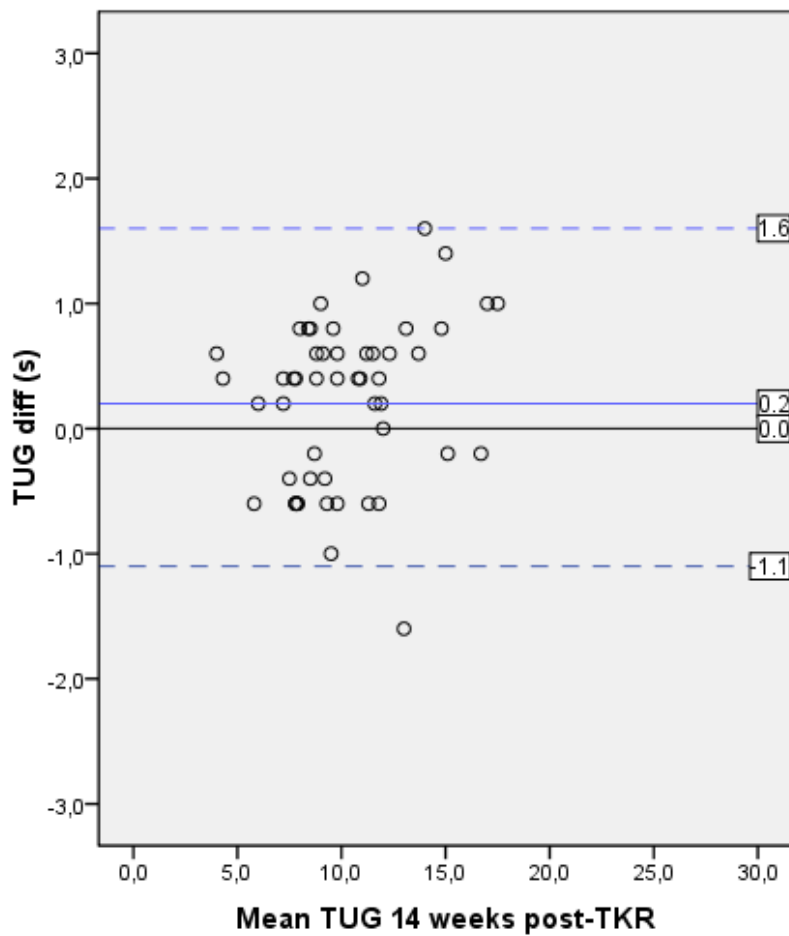
Figure 7.1a shows that data points are scattered relatively evenly above and below zero, showing no specific bias for the upper or lower limits. No systematic bias of one trial over the other is presented, as the difference between trials appears proximal to zero (0.02s).

Figure 7.1b Bland & Altman plot for TUG Test at 8 weeks post-TKR.



TUG: Timed Up and Go test; diff: difference amongst trial measurements; (s): seconds. According to Figure 7.1b, limits of agreement were narrower (± 1.3 s versus ± 1.6 s) before surgery than 8 weeks after surgery. However, better agreement was apparently revealed qualitatively at 8 weeks post-surgery (compared to pre-surgery), as more patients' data points are close to zero and data points are less scattered within this plot, in comparison to Figure 7.1a.

Figure 7.1c Bland & Altman plot for TUG Test at 14 weeks post-TKR.



TUG: Timed Up and Go test; diff: difference amongst trial measurements; (s): seconds.

Figure 7.1c showed that LoA appear to be acceptable for this TKR population, in general, scatter of data points that is well-contained. However, a systematic patterning bias towards the first measurement is presented for both operated and non-operated limbs, and which deviates from zero 0.2s.

The corresponding Bland and Altman limits of agreement plots for rectus femoris muscle CSA are presented in Appendix II.

7.5 Discussion

The purpose of this study was to assess reproducibility, single-measurement reliability, measurement error and levels of agreement for the indices of functional

(TUG Test), sensori-motor (JPE), neuromuscular (PF, EMG- Peak amplitude) and musculoskeletal performance (CSA of the rectus femoris muscle), for both operated and non-operated limbs, during the three different testing occasions spanning surgery and rehabilitation for patients undergoing TKR [pre-surgery (0 weeks), and at 8 weeks and 14 weeks post-TKR]. Findings of this study suggested that none of the indices of functional, sensori-motor, neuromuscular or musculoskeletal performance had shown systematic carry-over or learning effects when intra-session group mean changes were assessed statistically using ANOVAs, except for a couple of cases in Peak Force and JPE (as indicated in Table 7.2). This is a novel study of the single-measurement reliability, reproducibility (including MDC) and estimates of agreement (LoA) of such a wide selection of outcomes concomitantly, in a TKR population.

It could have been argued conceptually that indices of performance might have shown more variability prior to surgery than afterwards, because rehabilitation and concomitant physiological recovery would have facilitated a patient having greater consistency in skilled performance. Similarly, it is plausible that the operated limb, which could have been expected to undergo disease-related physiological de-conditioning during the period of time leading up to surgery especially, might have shown greater performance' variability than the contralateral limb. As depicted by the indices of measurement reproducibility, CV % and MDC, as well as by the characteristics of LoA, the contralateral limb indeed appeared to have shown less variability in its performance compared to that of the operated limb for the majority of outcomes. However, in contrast to tentative expectations for the study's findings, post-TKR single-measurement reliability and reproducibility characteristics for most outcomes did not appear qualitatively to be superior to those measured prior to surgery. From another perspective, since different interventions (as described in the main thesis study, Chapter 8) were implemented in the sample groups, heterogeneous responses might be observed, whereas before surgery, the TKR population's performance may have been expected to be less variable. As such, it would appear outcomes did not offer improving measurement precision as recovery and rehabilitation progressed for these patients and fluctuations were relatively stable. Thus, specifically protocols for measuring quadriceps' PF and rectus femoris muscle' CSA before surgery would need to use the mean score of multiple trials

from the same individual in order to reduce the error variability of measurement to match that after surgery.

Excellent reliability was demonstrated for each of the outcome measures of functional, neuromuscular (PF and Peak amplitude), and musculoskeletal (CSA of rectus femoris in contraction) performance. Based on the ICC scores, which had been reported as 'moderate' from 0.50 to 0.69, 'high' from 0.70 to 0.89 and 'very high' from 0.90 and above (Sole *et al*, 2007), the findings of this study showed that the TUG Test, and the PF for the quadriceps for both the operated and non-operated limbs, had achieved 'very high' reliability (ICC > 0.94) on all the testing occasions. Similar findings regarding the high levels of reproducibility of the TUG Test had been reported by Steffen *et al* (2002). Results are in accordance to the available literature for PF, as excellent reliability for this index of performance has also been reported (Kean *et al*, 2010). Moreover, single-measurement reliability levels of between 0.77 to 0.90 have also been reported for EMG peak amplitude of the knee extensors in relevant studies (Bamman *et al*, 1997; Viitasalo & Komi, 1975). Finally, this study's findings are in accordance with the literature on the reproducibility characteristics of CSA for the rectus femoris muscle (ICC ranged from 0.87 to 0.99) (Bembem, 2002; Lima *et al*, 2012). With the observed ICC values all being > 0.70, the TUG, PF, EMG-amplitude and CSA could all be considered reliable enough to be used clinically. A value of 0.70 is the minimum recommended level at which an outcome measurement associated with a given test can be used to evaluate the performance of individuals, as well as those of groups in research (Streiner *et al*, 2014).

Moderate to high (ICC: 0.60 - 0.83) single-measurement reliability was demonstrated for JPE sensori-motor response measurements. The knee joint position sense measurements were slightly poorer for the pre-surgery assessment occasions (compared to post-surgery). Moreover, it was also observed that the non-operated limb showed lower levels of single measurement reliability than that of the operated limb. This may be explained by the fact that in most patients, both limbs appeared with OA degenerations, but the limb mostly affected was selected first for TKR by the Orthopedic surgeon. Interestingly, no between-knee difference in sensori-motor performance was found in patients with unilateral knee OA, implying that this impairment is not exclusively local (Sharma *et al*, 1997). A number of

studies have demonstrated a positive relationship between knee pain and impaired proprioceptive accuracy (Bennel *et al*, 2003; Lund *et al*, 2008; Hall *et al*, 2006). Knoop *et al*, (2011) in their narrative review have reported good inter-session reliability levels for JPE (ICC > 0.70). Baert *et al*, (2017) in a sample of knee OA and healthy controls showed higher levels of single measurement reliability (ICC: 0.65 – 0.95). Poorer levels were reported for the 70 °, than the 45 ° or 20°. In the current study, the mid-range position of 60 ° also showed lower levels of reliability (ICC: 0.69 – 0.76), than the more extended 25 ° position (ICC: 0.68 – 0.83) of the affected side. Therefore, the more extended positions should be used during measurement by clinicians and researchers. In accordance with the literature the mid-range positions are more challenging in sensori-motor disturbances for knee OA patients, and could therefore be taken into consideration by clinicians during exercise programmes (Baert *et al*, 2013). To the author's knowledge no systematic review and/or meta-analysis of the studies investigating sensori-motor performance in knee OA patients has been done, to determine a more enlightening measurement protocol for joint position tests in clinical practice.

Bland & Altman plots were not exhaustively presented for all indices but indicatively for TUG and CSA_{RF}. In addition to excellent consistency, the TUG also showed good levels of agreement with low bias, measurements evenly scattered and relatively narrow LoA (<+/- 1.6s) in the Bland & Altman plots. Measurements pre-surgery and at 8 weeks post-surgery did not show any bias for one trial over another, whereas at 14 weeks a bias of the first trial over the second was shown, with a deviation of 0.2s away from zero. Both the TUG Test and the rectus femoris muscle' CSA outcome measures have shown good overall reliability when used for assessments in a TKR population. Similarly, it is difficult to comment on the suitability and utility of the rectus femoris muscle CSA's agreement' limits for clinical use in patients undergoing TKR, as direct comparisons cannot be made with the literature currently.

The functional performance of a patient post-TKR is likely to decrease during the early post-operative phase, or increase after the first two months to the extent that there would be a change in score (a raw effect size) of more than 3s on the TUG in the time-frame of six weeks (Mizner *et al*, 2005). Within the findings of this study (Table 7.2), a two-fold greater change score of 6.2s was found within the time-frame

of 14 weeks compared to the study by Mizner *et al* (2005). The $MDC_{95\%CI}$ value for the TUG was calculated to be 1.7s based on the responses of the 52 participants in this study. Therefore, clinicians should look for time changes in a patient's performance (especially so if the patient scores close to the group mean response of the current sample of patients) that are either greater (for example, to confirm the efficacy of a conditioning intervention) or less (for example, to confirm physiological de-conditioning) than this critical value in order to be confident (to 95 % levels) that a true change has occurred in their patient's functional and balance capabilities. However, attempts to generalise from these findings might suggest that in contrast to the findings within the current study, slightly larger MDC values might need to be deployed as gauges of critical changes in patients' performances, because the wider clinical literature has reported the imperative to use a MDC of ~2.5s for it to be relevant to patients' ADL (Kennedy *et al*, 2005).

With respect to the sensori-motor performance of a patient post-TKR, a limited number of studies in the literature have investigated joint position sense measures. While improvements (1.5 °) have been reported by some studies following TKR (Barrett *et al*, 1991; Swanik *et al*, 2004), others have reported no difference (Pohl *et al*, 2015). In the current study, the raw ES for group mean JPE scores during the period of surgery and rehabilitation was < 13.0 °. However, a $MDC_{95\%CI}$ of 20.4 °, and a large CV % (~45 % to 87 %) were found. Therefore, the observed precision of measurement (based on MDC and CV %) criteria that would be likely to correctly discriminate (with 95 % confidence levels etc.) changes for both an individual patient (especially for a patient who's scoring close to the group mean score), and for the group of patients as a whole, suggests that during the 12 weeks' time period of rehabilitation, relatively large measured changes in performance (large ESs over 20°) would be needed to confer confidence in the gains made by the patient(s) and the in the potency of an intervention. In a recent study (Baert *et al*, 2017), investigating reliability of sensori-motor performance tests, a $MDC_{95\%CI}$ of 8 ° was reported in a small sample (n = 8) of knee OA patients. Reliability and measurement precision differences could be explained by the raters' skills or personal characteristics, the number of trials analysed (two in the aforementioned study vs three in the current study). The measurement protocol employed was the same, as in both studies, as the active repositioning method was used. However, a plurimeter was used in the study by Baert *et al* (2017) (versus a baseline bubble inclinometer in

the current study) to measure repositioning error, fact that may also impact on the measurement precision.

In terms of neuromuscular performance, most of the studies have shown that knee extensors' muscle strength of a patient post-TKR is likely to decrease during the early post-operative phase to the extent that there would be a loss of ~35 N for the PF in the time-frame of three months (Mizner *et al*, 2005; Stevens-Lapsley *et al*, 2010). Within the findings of this study, a gain score of ~20 N was found within the time-frame of 14 weeks. The $MDC_{95\%CI}$ value for the PF was calculated to be 8.6 N, based on the responses of the 52 participants in this study. Therefore, clinicians should look for, and only rely upon, changes in performance, which exceed this criterion score (ESs over ~9 N) in a patient's muscle strength to be confident on the efficacy of an intervention, based on the observed MDC and the CV %.

However, whilst relatively high measurement reproducibility and moderate ranges of CV % scores were recorded for TUG Test, rectus femoris muscle' CSA, and quadriceps muscle strength (PF), relatively measurement reproducibility was shown for measures of proprioception (JPE). Thus, the large CV % scores and correspondingly low measurement reproducibility associated with proprioception might suggest that for individual patients, relatively large measured changes in performance would be needed to confer confidence in the efficacy of an intervention, or indeed, de-conditioning if that was to have occurred, and there had been a concomitant reduction in measured sensori-motor performance. Therefore, within the context of the clinimetric qualities of measurement reliability and reproducibility, a hierarchy of measurement performance could be offered tentatively, with the TUG Test, rectus femoris muscle' CSA and quadriceps' PF offered as potentially the best-performing outcomes, and with JPE and EMG-amplitude as the worst-performing outcomes when assessed in this cohort of patients awaiting and undergoing TKR and rehabilitation.

As alluded to earlier in the context of appropriate use of MDC criteria, any generalisation of the current study's findings to the wider population of TKR patients should be made with caution. In terms of clinical relevance of this study's findings to the main study (Chapter 8), the selected indices that have been considered, offer sufficient measurement reproducibility for both operated and non-operated limbs, for

them to be recommended reasonably for use in the main RCT study to demonstrate potential efficacy of training programmes.

In clinical practice, a change score is based on, in general, the difference between pre-treatment and post-treatment scores, and the treatment period may extend to several weeks for a TKR patient. The need for effective evaluation of differences between operated and contralateral limbs in performance capabilities within a single test session, and the evaluation of the effectiveness of treatment interventions over time (efficacy) is always considered important by clinicians and clinical scientists. Each research application involving critical levels of measurement precision (e.g. intra-session vs. inter-day) represents unique challenges in the selection of an appropriate test protocol to enable sufficient precision of measurement to facilitate confident discrimination between performances (Altman, 1991; Mercer & Gleeson, 2002).

The assessment of single-measurement reliability for a given outcome measure, within populations possessing particular homogeneity/heterogeneity characteristics, would ideally be conducted over various time-periods (i.e. comparisons amongst intra-session, intra-day and inter-day periods of time). However, in practical terms, as is the case within this thesis, this ideal scenario for assessing the precision of measurement is not always possible. Shorter test-re-test periods, such as those within the same session (intra-session) as in this study, have the risk of bias caused by the subject recollecting his/her performance. Based on evidence within the literature, there is also an assumption that the random measurement error detected during this shorter period of evaluation, will be an underestimate of what might be observed over longer periods of time, and which might ultimately affect the correct interpretation of an individual patient's changes in performance capacity during longitudinal intervention studies and rehabilitation programmes.

Inter-day variability in neuromuscular performance has been reported to be greater than intra-day variability (Wyse *et al*, 1994). This suggests that the calculation of reliability based solely on intra-day measures may be an overestimate that fails to account fully for the biological variability inherent in leg strength test performance (Gleeson *et al*, 2002; Minshull *et al*, 2009). Methodologically diverse investigations have examined the reproducibility of PF of the thigh musculature subsequent to

volitional muscle activation and have reported intra-day coefficients of variation of 4.1 % (Viitasalo *et al*, 1980) and inter-day CV % scores of 6.6 % (Gleeson *et al*, 2002) as an aggregate for the knee extensors and flexors. During intra-session assessments of PF, CV % has been found as 3.5 ± 1.9 %, whereas during inter-day assessments the CV % has been found to be as high as 8.5 ± 3.3 %, in asymptomatic subjects. Corresponding scores for CV % for inter-day assessments has been found to be 6.6 ± 3.0 %, in symptomatic subjects, such as in patients with chronic renal disease (Gleeson *et al*, 2002).

However, in the current study, involving symptomatic patients undergoing TKR, the CV % for PF scores was found to range between ± 4.2 % and ± 11.4 %, while MDC scores (at 95 % confidence levels) involved an absolute score of ± 8.6 N. Therefore, because of the inflated magnitude of error scores noted for patients undergoing TKR in this study compared to those that have been considered in the literature, the capability clinimetrically to detect individual patient-related changes in performance from estimates of error variability based on intra-session scores (as performed within this study) might be especially limited. Indeed, even if logistically, there had been the capability within the current study to have estimated outcome error variability, reproducibility or measurement precision based on inter-day random variability in scores, then potentially, the usefulness of using single measurements to discriminate between changes in an individual patient's performance capability over time would have been compromised even more so, given that inter-day variability is most likely greater than intra-session variability.

As this was a single researcher PhD study, inter-rater reliability was not investigated. The sample size was relatively small and as such, the methodological quality of the study would be considered poor if assessed using the COSMIN quality criteria, and the quality of evidence would be deemed indeterminate. However, it could be argued that having a higher sample size may have resulted in lower agreement with the increased possibility of higher variances in the participants. The participants in the current study were recruited for the main thesis RCT study, where TKR surgery and distinct rehabilitative interventions (experimental and control) took place from the first to the second and third test session. Therefore, the degree of variability in the second and third session may be different due to the response of the subgroups to the distinct interventions implemented. The researcher was not

blinded to the prior findings of the outcome measures under investigation, nor blinded to the reference standards of selected measures within the literature.

Nevertheless, while these kinanthropometric issues are of particular concern for the individual patient and the correct interpretation of his/her changes in performance over time, these points of discussion should not necessarily be an overriding concern for the effective design of group-based investigations, such as in the case of this thesis' main study involving a RCT (Chapter 8). In the latter scenario, as long as the balance of criteria are in place for an outcome measure being able to correctly detect an expected (e.g. based on precedent in the literature, 'pilot' study, or selected minimal detected change for clinical utility) group mean change in an outcome over time (based on a particular number of patients within the sample), while achieving prescribed levels of probabilities for Type-I and Type-II error rates, then there is likely to be an acceptable experimental design sensitivity. Ultimately, the latter issues might be independent of the considerations for measurement relating to individual patients.

From the results of this reproducibility and single-measurement reliability study carried out on a relatively small group of patients undergoing TKR, the following conclusions have been drawn to impact the main study of the thesis, clinical practice and future research: All the outcome measures studied, demonstrated excellent single-measurement reliability ($ICC > 0.70$), with the exception of JPE that showed moderate to high levels of reliability. No considerable systematic bias was noted amongst trials to suggest carry over or learning effects. Bland & Altman plots also showed acceptable agreement for indices of functional and musculoskeletal performance. On this basis, the selected indices can be recommended for use within group-based experimental designs and at the level of an individual patient. Furthermore, from the perspective of this study's findings for measurement reproducibility, changes in patients' performance capabilities that exceed the confidence limits associated with MDCs and corresponding CV %, identified within this study, will show real effects during the clinical assessments of individual patients undergoing TKR surgery. A change of at least $\pm 1.7s$ is required on the performance of the TUG Test, in order to demonstrate a real change in the functional ability of an individual patient, or in a wider context, of the group mean capability of a TKR population. A change of at least $\pm 8.6 N$ on scores for PF is required to demonstrate a real change in the knee extensors neuromuscular

performance of an individual patient undergoing TKR. A change of at least 20.4 ° is required during the assessment of JPE to demonstrate a real change in the sensori-motor responses. Similarly, a change of 35.6 mm² in the rectus femoris muscle' CSA is required to demonstrate a real change in musculoskeletal performance.

Chapter 8 - Main Study

What are the effects of enhanced sensori-motor exercise training on indices of functional, balance-related, sensori-motor, neuromuscular and musculoskeletal performance compared to functional exercise training (usual care) in patients following total knee replacement?

Abstract

Background and Purpose: Despite partial improvements in functional mobility and balance, the rate of falls remains high for patients following total knee replacement (TKR). Sensory-motor training (SMT) techniques have been considered as a targeted approach to counteract relevant deficits. Aim of this study is to explore the effects of enhanced sensory-motor exercise training (ESMET) compared to usual care functional exercise training (FET) on functional performance in patients undergoing TKR.

Methods: A single-blind randomised controlled trial. Fifty-two patients electing to undergo TKR were recruited from GR Orthopedic University Hospital of Rion, Patras. Patients were randomised to either ESMET [intervention] or FET [control]. Both groups received a 12-week, home-based programme prescribed for 3 - 5¹ (35 - 45 minutes-session⁻¹). The primary outcome measure was the Timed Up and Go (TUG) Test and the secondary outcomes were balance, joint position error, quadriceps peak force (PF), rectus femoris cross-sectional area (CSA_{RF}), knee ROM and self-reported indices of function (Knee Outcome Survey Activities of Daily Living Scale [(KOS-ADL), KOOS, SF-12], QoL and pain. Patients were assessed on three separate occasions pre-surgery [0 weeks]; 8 weeks post-surgery; 14 weeks post-surgery.

Results: Statistically significant changes in group mean scores for the primary outcome measure favour the ESMET compared to the control group: TUG Test (7.8 ± 2.9 s vs 4.6 ± 2.6 s); balance (2.1 ± 0.9 ° vs 0.7 ± 1.2 °); joint position error (13.8 ± 7.3 ° vs 6.2 ± 9.1 °); KOS-ADL Scale (44.2 ± 11.3 vs 26.1 ± 11.4); pain (5.9 ± 1.3 cm vs 4.6 ± 1.1 cm) ($F_{(2,98)} > 6.2$; $p < 0.005$). Changes in group mean scores in quadriceps muscle measurement favour the ESMET compared to control training: (PF (25.1 ± 18.5 N vs 12.4 ± 20.8 N); CSA_{RF} (2520.2 ± 1010.3 mm² vs 1567.0 ± 761.7 mm²); SF-12 (16.2 ± 4.1 vs 11.8 ± 8.0), respectively; net group mean changes in performances between pre-surgery (0 weeks) and 14 weeks post surgery; $p < 0.005$). Patterns of improvement for the ESMET group over time were represented by a relative effect size range of 1.0 to 6.5.

Conclusions: Overall, the magnitude of improvements in functional, balance, sensory-motor performance, quadriceps peak force and muscle size endorses using

enhanced sensori-motor exercise training as an effective mode of rehabilitation following knee replacement surgery. Findings need to be interpreted with caution due to the single-blind nature of the study design.

8.1 Introduction

Within Europe, more than 0.1 % of national populations elect to undergo total knee replacements (TKR) annually (www.njrcentre.org.uk/njrcentre/Patients/Jointreplacementstatistics/tabid/99/Default.aspx, 2017; OECD Health Statistics 2014; OECD/European Union, 2016; <https://www.efort.org/total-knee-replacement-international-differences-in-frequency-and-surgical-technique>) with 20 - 30 % of patients dissatisfied with the outcome at the end of the pathway of care (Hurley *et al*, 2010). Patients' underlying capacity to generate force and perform tasks does not fully recover until twelve months post-surgery (Stevens-Lapsley *et al*, 2011; Yoshida *et al*, 2008). Surgery has been shown to be optimal for pain relief compared to physical rehabilitation. However, two thirds of patients randomly-allocated to rehabilitation showed clinically meaningful improvement in their symptoms (Skou *et al*, 2015). This questions why alternative conservative treatments are not being fully exploited and suggests that postoperative function can be enhanced. Given the continued increase in the number of TKRs being performed, it becomes essential to identify cost-effective strategies to diminish the need for revision procedures and to enhance the quality of rehabilitation (Lavernia *et al*, 2006; Moffet *et al*, 2004; Thomas, 2003; Westby *et al*, 2008). The provision of exercise with a functional focus (Moffet *et al*, 2004; Frost & Lamb, 2002), is the most common clinical approach in the rehabilitation of TKR patients reported by physiotherapists (Naylor *et al*, 2010). In Greece, from consultation with physiotherapists in the field, it became apparent that a significant percentage of TKR patients (~57 %) are discharged from hospital towards the patient's home environment, with some vague advice on transfers and gait, and that a functional exercise programme had always been prescribed (Moutzouri *et al*, 2013). Patient experiences and pathways of care that lack coherence and extent may contribute to dissatisfaction after surgery (Nam *et al*, 2014), but post-operative healthcare costs increase annually, with significant economic impact (£7,000 [€7,980] per patient over a five-year follow-up period) (Parvizi *et al*, 2015).

Following hospital discharge, patients encounter challenges in activities of daily living that demand high levels of functional mobility, to avoid potential falls' risk. Although TKR seems to improve balance and falls-incidence, inferior sensori-motor performance compared to aged-matched controls fuels controversy about whether capabilities are actually superior to those of the severe osteoarthritic non-operated.

A year after TKR, the main cause of falls has been shown to be tripping and stumbling, and the majority of falls have taken place during walking. In most cases, the main cause of stumbling was minor (Tsonga *et al*, 2016). But the adjustment, reaction speed and muscle strength required to overcome the obstacle is beyond the ability of the elderly person. The process of early active exercise in joint rehabilitation is significantly hindered by the patient's inability to contract surrounding musculature (arthrogenic muscle inhibition (AMI), neural activation deficits linked to swelling, pain or structural damage), as is common after joint surgery (Dakin *et al*, 2012). Therefore, targeted rehabilitation strategies need to be implemented in the early (post-acute) phase after surgery to prevent AMI intruding (Bade *et al*, 2011; Stevens *et al*, 2003). The weakness and delayed activation of quadriceps have been identified as the major cause of activity limitations post-TKR and are associated with post-surgery quadriceps muscle' strength deficits losses of up to 60 % compared to baseline levels, especially for the operated limb (Hopkins & Ingersoll, 2000). Therefore, functional rehabilitative training has conventionally incorporated muscle strengthening stimuli, and has been mostly delivered using an isometric or a concentric mode within functional weight-bearing exercises (Valtonen *et al*, 2009; Shabbir *et al*, 2017; Liu *et al*, 2018; Mizner *et al*, 2005). Nevertheless, this approach to rehabilitation has not been capable of either counteracting the post-surgery deficits in strength effectively or of favourably altering the movement patterns of the knee during functionally important tasks for up to six months after surgery (Liu *et al*, 2018; Mizner *et al*, 2005).

In the US, 2.2 million elderly patients received treatment for fall injuries in 2009 (Web-based Injury Statistics Query and Reporting System [WISQARS]). The relevant medical costs were reported to be 23.3 billion dollars in 2008, and it is predicted that this will increase to 55 billion dollars worldwide in 2020. It follows that falls are a socially important issue, and research into methods of preventing falls by improving muscle strength and balance ability, is thereby warranted.

Falling after TKR can cause potentially devastating problems, including periprosthetic fracture or severe soft-tissue injury (Weber *et al*, 1999). In a study by Kearns *et al* (2008) from a consecutive series of 1,341 TKRs, 78 patients (7 %) reported falling. Slightly higher numbers of fallers (~11 %) have been reported in an observational study by Swinkels *et al* (2009). Median time from TKR to a fall was

507 days (range, 11 - 2852 days). Seventeen of the seventy-eight patients (~22 %) had fallen within eight weeks of their TKR. From the analysis of the available literature (Moutzouri *et al*, 2016b), it became apparent that although TKR improves balance (up to 60 %) and falls-incidence (by switching ~55 % of pre-operative fallers to post-operative non-fallers), inferior sensori-motor performance compared to aged-matched controls (Pap *et al*, 2000) fuels controversy about whether capabilities are actually superior to those of the severe osteoarthritic non-operated (Bascuas *et al*, 2013; Yakhdani *et al*, 2010). Functional balance-related difficulties might persist in knee replacement patients, unless novel targeted rehabilitation could be shown to address joint instability and compromised balance in remnant muscle and ligament receptors (Gage *et al*, 2008).

Sensori-motor training is based on the concept that instead of addressing isolated muscular strengthening, the real emphasis should be given in enhancing the CNS's functional capability in regulating movement in order to reach proper muscle firing patterns for maintaining dynamic joint stability (Riemann & Lephart, 2002). Sensori-motor training emphasises postural control and progressive challenges to the SM system to restore normal motor programmes in patients with chronic musculoskeletal pain. Depending on the desired motor outcome, proper motor firing patterns mean optimising which muscles will fire, how strongly and quickly firing will occur for efficient energetics, and what motor patterns and postures will have been adopted by a joint system. Neuromuscular control requires efficient co-ordination of strong muscles and interventions that deliberately address sensori-motor and locomotor control. According to the studies by Piva *et al*(2010) and Liao *et al*(2013), focal SMT may provoke safe post-surgery milestones of functional recovery compared to contemporary functional therapy when started at two months following TKR (Moutzouri *et al*, 2016a). However, following hospital discharge, patients encounter challenges in ADL that demand high levels of functional mobility, in order to avoid potential falls' risk. Therefore, early implementation of SMT programmes should be considered and this imperative would become the focus of the main study within the thesis. Consequently, the term "enhanced sensori-motor" exercise training programme encompasses the following characteristics: An early initiation of self-managed, enhanced sensori-motor exercise training which is thought to produce safe functional recovery milestones, and which would be considered to be occurring earlier compared to usual care therapy programmes in patients following TKR..

From the findings of a relevant recent systematic review, it became evident that an important question regarding the effectiveness of a usual care programme in comparison to that of usual care with the addition of SMT in the rehabilitation process of knee replacement, remained unanswered, as integrated exercise had not been introduced and the volume of exercise had not been controlled and delivered equally amongst research groups (Moutzouri *et al*, 2016a). Moreover, the effectiveness of implementing such training programmes has not been established within environments requiring self-managed care by patients, despite the fact that many international health care' systems have adopted the latter approach as a preferred mode of exercise delivery (Chimenti & Ingersoll, 2007; Froimson, 2013).

Eccentric exercise has been shown to mitigate deficits in strength and muscle size at one year post-TKR (La Stayo *et al*, 2009). Therefore, exercise rehabilitation is a key component in reversing the decline in muscle performance of patients, which has been observed up to three months post-surgery (Mizner *et al*, 2011; Yoshida *et al*, 2008). Not surprisingly, muscle strengthening is an important aspect of TKR rehabilitation, aiming to improve the dynamic stability and lessen the potential falls' risk (Matsumoto *et al*, 2014; Moreland *et al*, 2004). Effective rehabilitation strategies to address quadriceps' muscle weakness after TKR should target the sources underlying its early manifestation. However, it is currently under-researched as to whether or not rehabilitation with increased focus on sensori-motor conditioning, offers sufficient stimuli to enhance 'motor' or strength performance capabilities. Ahmed (2011) found increased quadriceps' muscle-force generating capacity by implementing SMT in knee OA patients. It has been suggested that SMT increases coordination between muscle groups and improves the response to sensorial information. In SMT, the patient progresses through exercises in different postures, bases of support, and challenges to balance accompanying changes in the positioning of their centre of gravity. So, each exercise elicits automatic and reflexive muscular stabilisation challenging the patient to maintain postural control under a variety of situations. Stimuli offered by this type of training are proposed to enhance unconscious motor responses by targeting joint and muscle receptors. In this way, SMT activates central mechanisms to regulate movement patterns, reach proper muscle firing' patterns and restore dynamic joint control. Therefore, one of the novel aims of the main study was to investigate indirectly whether the hypothesised

“motor” changes elicited by enhanced SMT, would actually be delivered in patients undergoing TKR.

With increased strength performance capabilities, that might plausibly offer concomitant improvements in functional capabilities, it would be important clinically to know to what extent these hypothesised transformational changes associated with SMT, might be correctly perceived by patients, using appropriate PROMs of psycho-physiological performance. A further aim was to describe intervention-related patterning of changes amongst the study’s secondary outcomes and to see the extent of congruency with those of primary outcomes and the mechanistic basis for any improvements in functional capability.

The purpose of this study was to compare the effects of early initiation of self-managed, enhanced sensori-motor exercise training with those of equivalently-delivered functional exercise training (usual care) on patients’ functional performance following TKR.

8.2 Research Hypothesis

Hypothesis 1:

- *Null (Ho):* There will be no difference in the effects of early initiation of self-managed, enhanced sensori-motor exercise training with those of functional exercise training (usual care) on indices of functional performance (TUG Test) in patients following TKR.
- *Alternative:* There will be a difference in the effects of early initiation of self-managed, enhanced sensori-motor exercise training with those of functional exercise training (usual care) on indices of functional performance (TUG Test) in patients following TKR.

Hypothesis 2

- *Null (Ho):* There will be no difference in the effects of early initiation of self-managed, enhanced sensori-motor exercise training with those of functional exercise training (usual care) on balance-related, and sensori-motor performance.

- *Alternative:* There will be a difference in the effects of early initiation of self-managed, enhanced sensori-motor exercise training with those of functional exercise training (usual care) on balance-related, and sensori-motor performance.

Hypothesis 3:

- Null (Ho): There will be no difference in the effects of early initiation of self-managed, enhanced sensori-motor exercise training with those of functional exercise training (usual care) on secondary outcomes of neuromuscular (muscle strength) and musculoskeletal performance (knee ROM and muscle size) in patients following TKR.
- *Alternative:* There will be a difference in the effects of early initiation of self-managed, enhanced sensori-motor exercise training with those of functional exercise training (usual care) on secondary outcomes of neuromuscular (muscle strength) and musculoskeletal performance (knee ROM and muscle size) in patients following TKR.

Hypothesis 4:

- Null (Ho): There will be no difference in the effects of early initiation of self-managed, enhanced sensori-motor exercise training with those of functional exercise training (usual care) on secondary patient-reported outcome measures of functional and psycho-physiological performance.
- *Alternative:* There will be a difference in the effects of early initiation of self-managed, enhanced sensori-motor exercise training with those of functional exercise training (usual care) on secondary patient-reported outcome measures of functional and psycho-physiological performance.

8.3 Methods

A single-blind randomised controlled trial (RCT) was undertaken at a primary care University hospital in Greece (International Standard Randomised Control Trial Registration: ISRCTN12101643) having been approved ethically by institutional Committees (University Hospital of Patras; Queen Margaret University Edinburgh, UK [7052/4-7-2011] (Appendix V).

8.3.1 Participants

Consecutive patients (May 2012 - May 2014) undergoing primary standardised cemented TKR (single surgeon; 15-years' experience of knee replacement; 50 knee

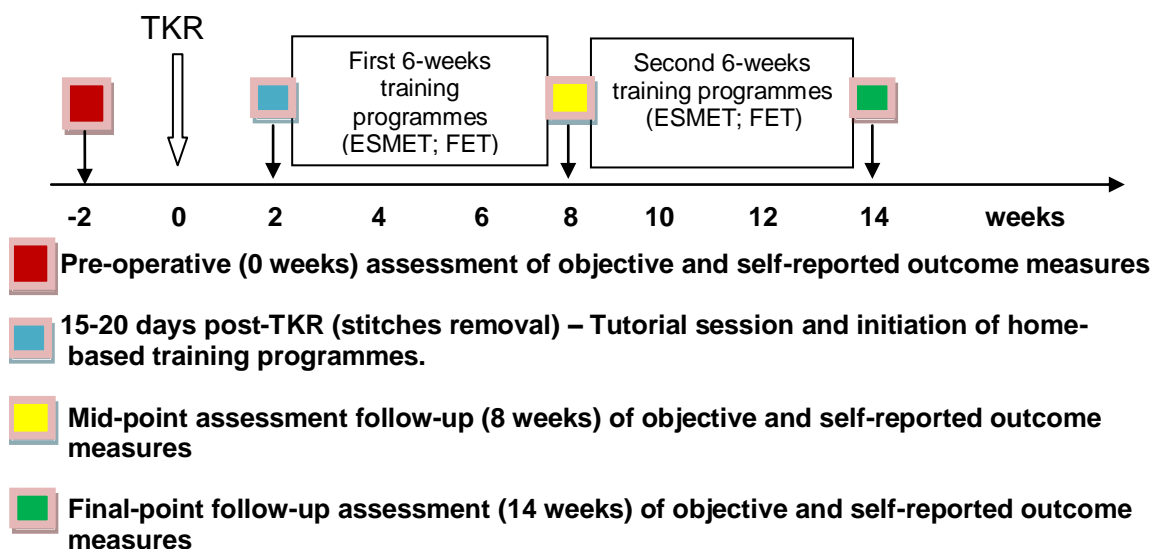
replacements per annum) were invited to participate in the study and were screened for study eligibility (ambulatory; clinical and radiological findings of advanced osteoarthritis; primary total knee replacement). Patients with neurological conditions, such as peripheral neuropathy, Parkinson's disease or multiple sclerosis, and vestibular disorders that might affect balance and those who were considered unable to communicate or follow instructions were also excluded from the study. After receiving a complete description of the study, all the patients gave written informed consent (Appendix III, IV).

8.3.2 Procedure Outline The procedure outline of the study is illustrated in Figure 8.1.

The study included a three phase intervention with:

- 1) 2-week post-surgery care pathway;
- 2) 6-week intervention phase with either enhanced sensori-motor exercise training (ESMET) or functional exercise training (FET), and
- 3) further 6-week intervention phase with either ESMET or FET

Figure 8.1 Diagram showing the experimental procedure outline of the study.



Exercise training and progression

A standardised post-surgery care-pathway for all patients comprised of two weeks of hospital-based bedside and preparatory physiotherapy that was delivered by two physiotherapists who were independent of the study. After discharge, they were

encouraged to continue the same exercise protocol and gait practice at home. A 12-week programme of self-managed, home-based exercises designed to enhance functional capabilities (modified from Piva *et al*, 2010) was initiated at ~2 weeks after surgery (range 15 - 20 days). At the programme's inception, an experienced physiotherapist (principal investigator) conducted an educational training session with patients in order to teach the key features and characteristics of safe delivery of the exercise programme that they would follow at home. Patients' training programmes were further prescribed using a standardised illustrated guidebook of 14 exercises to regulate exercise-specific dosages. From week 3 to week 8, patients undertook 5 exercise sessions per week, as it has been underscored that in the early (post-acute) phase post-TKR, enhanced strategies within the home-based rehabilitation involve frequent mobilisation and strengthening exercises to avoid AMI that plagues this patient population (Bade *et al*, 2011; Stevens *et al*, 2003). Sessions increased progressively in duration from 35 to 45 minutes, incorporating progressively longer durations of walking from 10 to 20 minutes. At the end of 8 weeks, the first follow-up assessment session was performed at the hospital premises by the principal investigator. Weeks 9 to 14 required patients to complete 45-minute sessions of exercise, 3 times per week. The level of difficulty was progressed by adjusting exercise intensity (10 %) to calibrate with weekly changes in each patient's strength capability.

Patients' compliance with the prescribed intensity, duration and frequency of exercise was verified by 7-day recall activity diaries and a relevant questionnaire (McCarthy *et al*, 2004). Experimental and control groups were prescribed identical procedures, number of exercises and total programme' duration.

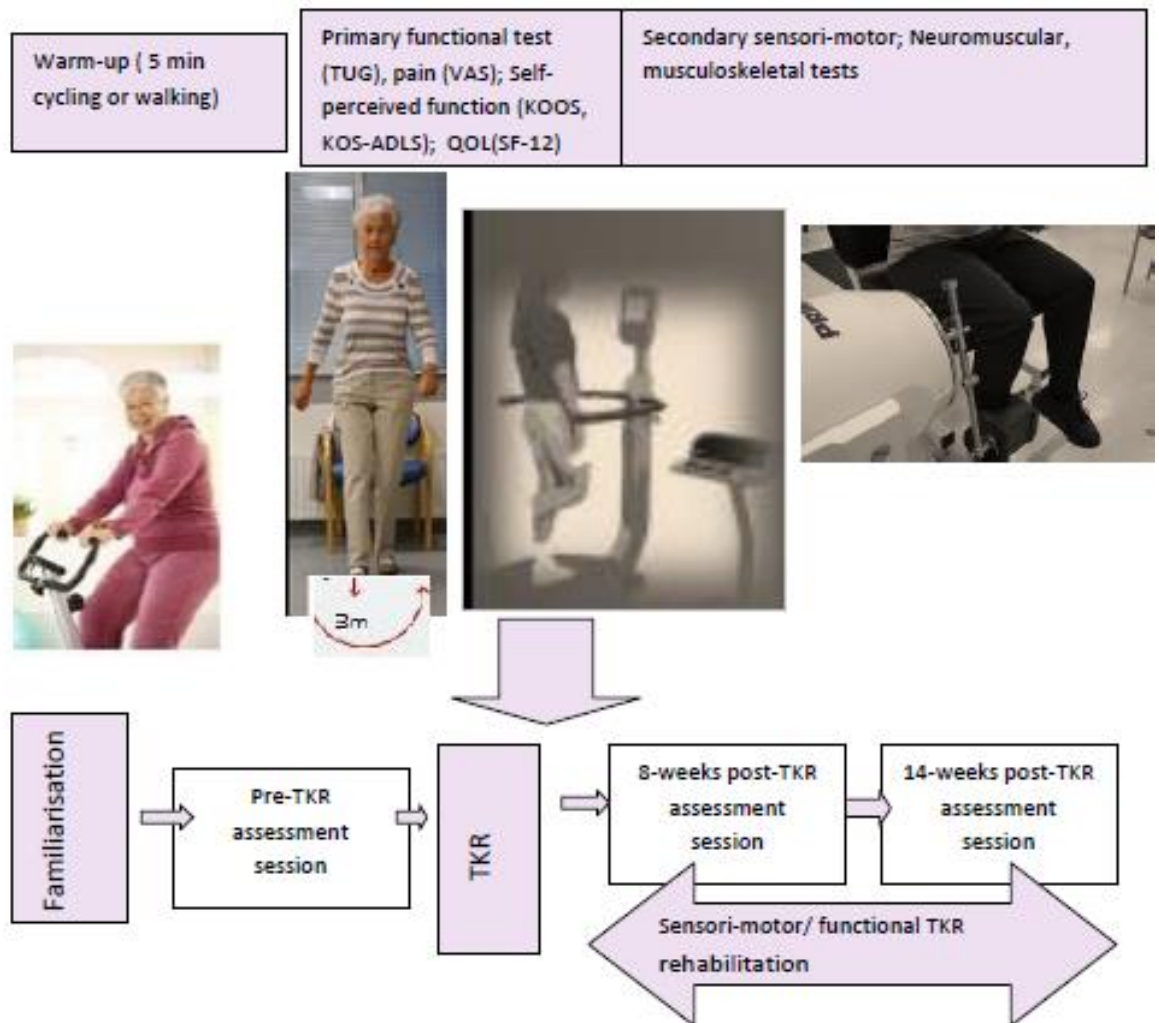
Level of physiotherapy interaction

As stated above, the principal investigator provided at ~2 weeks post-surgery a practical session individually with all patients to teach the exercise programme, explaining all safety precautions required and provide all necessary equipment for training (guidebook, theraband etc.). Due to the novel elements of the intervention (early implementation of SMT delivered in a home-based environment characteristics of ESMET) the Ethics Committee had advised for weekly assessing ESMET patients' safety and tolerance with the exercise programme. Therefore, patients from both groups were notified that the principal investigator would be

available once a week and were encouraged to drop-in if needed. However, patients in the ESMET group were encouraged to schedule appointments once a week for the first 6 weeks. Clinical oversight involved patients freely reporting effusion or discomfort and clarifying the delivery (accuracy, dose or safety) of the home-based exercises by telephone and by voluntary attendance *ad libitum*, for patients within both groups, within weekly scheduled clinical practical sessions with the principal investigator. Outcome data were collected by the study's principal investigator at pre-surgery (0 weeks), at eight weeks post-surgery (mid-point of the home-based therapy) and at 14 weeks post-surgery (end of the home-based therapy, primary end-point) (Figure 8.2). The CONSORT statement of the study is presented in Appendix IX.

The study's design involved an experimental manipulation of the contents' of the patients' usual twelve weeks of home-based, self-managed therapy to offer a comparison of the effects of usual care with those of a novel formulation of therapy, in which the duration of training sessions had been matched (time-matched). Allocation of patients to enhanced sensori-motor exercise training and functional exercise training (usual practice, control) groups was concealed to patients and investigators by means of independent (concealed coded listing maintained until after data analyses) confidential assignment delivered using block (n = 5) randomisation (computer generated random number listing; Excel 2007, Microsoft, Redmond, WA, USA). A physiotherapy undergraduate student accompanying the principal investigator at most of the assessment sessions informed patients of their group allocation.

Figure 8.2 Schematic design of the assessment occasions and protocol of trial.



Functional exercise training (FET) (Control)

Patients allocated to functional exercise training followed the usual home-based, self-managed post-surgery care, which encompassed pragmatically routine clinical practice based upon review of the literature (Moffet *et al*, 2004; Moutzouri *et al*, 2016b). As presented in Table 8.1 patients were taught and prescribed to perform 14 exercises within each session. Sessional demands comprised of routine elements of a warm-up activity, including range-of-motion exercises, stretch, or flexibility exercises; mobility exercises for lower extremities; strengthening exercises including isometric and concentric exercises for knee quadriceps and hamstrings and hip abductors; functional task-oriented exercises including stair climbing, squats and stationary cycling, treadmill or regular walking; and cool-down activities. Strengthening exercises in a concentric mode were performed with resistance

offered by an elastic theraband of medium resistance provided to all patients. Patients were encouraged to progress the exercises in a weekly basis, and increase the number of sets performed (3 - 5) when they felt the exercise was becoming easy enough.

Enhanced sensori-motor exercise training (ESMET)

Patients allocated to enhanced sensori-motor exercise training were prescribed a time-matched exercise programme with the control group. However, the emphasis was predominantly on enhancing sensori-motor functioning of patients. The exercises included novel formulations of agility and perturbation training techniques (i.e. side-stepping, backward stepping, and use of irregular foam laminations to offer focal sensori-motor stimulation over unstable surfaces) (Fitzgerald *et al*, 2011; Piva *et al*, 2010), which substituted for a proportion of training (50 % – 7/14 exercises) within usual practice. Since the sensori-motor exercises were designed to be delivered within a home-based environment, no specialised equipment was required. Exercise challenges and progression was achieved by using regular pillows to substitute for unstable surfaces, plastic cups for overcoming obstacles, and strategies such as bipedal to monopodal stance and eyes open to eyes closed in order to increase difficulty in maintaining or achieving balance. Again progression was encouraged for patients when the exercise was felt to become easy enough. Table 8.1 offers a description of both programmes of training. A more detailed illustration of the training programmes is offered in Table 8.2.

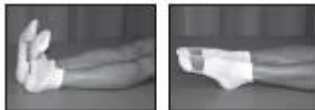
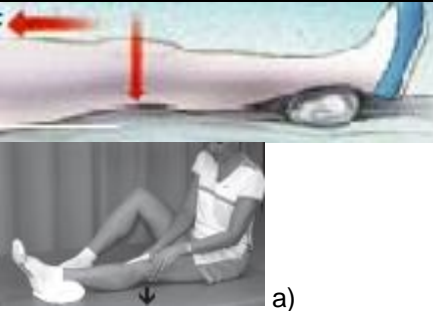
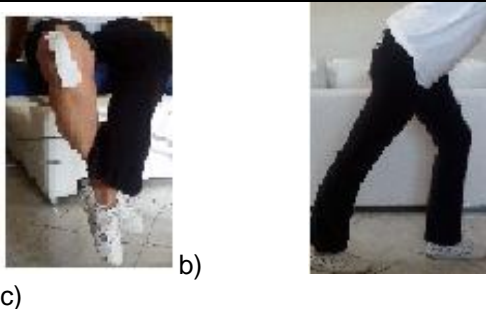

Table 8.1 Comparison of exercise training programmes applied in the enhanced sensori-motor exercise training group (intervention) with the functional exercise training group (control).










Exercise Training programme	Progression	FET	ESMET
Ankle ROM	10 - 20 rep.	x	
Knee ROM-Stretches 5 -10 min	3 - 5 rep.	x	X
Heel slide on wall	10 - 20 rep.	x	
Straight leg raise	3 - 5 sets of 10 rep.	x	
Quadriceps sets (short arc)	3 -5 sets of 10 rep.	x	X
Quadriceps strengthening with elastic band (sitting)	3-5 sets of 10 rep.	x	X
Quadriceps strengthening with elastic band (standing)	3-5 sets of 10 rep.	x	
Hamstrings strengthening with elastic band (standing)	3-5 sets of 10 rep.	x	
Abductors (side-lying)	2-4 sets of 10 rep.	x	







Sit-to-stand	10-20 rep.	x	X
Wall slides	10 - 20 rep.	x	X
Calf raises	10 - 20 rep.	x	
20-30 min walking or stationary cycling	5 - 20 min	x	X
Climb on a platform of stairs	10 - 30 steps	x	X
Marching	10-20 rep.	x	X
Side stepping	10-20 ft course length		X
Braiding activity	10-20 ft course length		X
Square stepping	10-20 ft course length		X
Walk over small obstacles	10-20 ft course length		X
Balance on foam	Two-to single-leg stance		X
Tandem Walking	10-20 ft course length		X

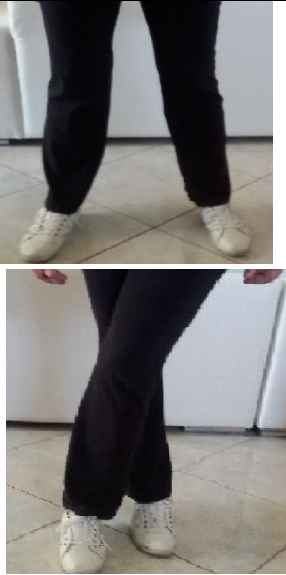



ESMET: Enhanced sensori-motor exercise training; FET: Functional exercise training; rep: repetitions.


Table 8.2 Physiotherapy training protocols as illustrated and prescribed in guidebooks for the FET and ESMET groups.

Functional standardized therapy programme performed by both groups (FET and ESMET).		
Exercise description	Exercise photo	Dose/Progression
1. Ankle ROM. Patient long sitting performs ankle plantar- and dorsi flexion.		Progress from 10-20 repetitions.
2a. Knee ROM-Stretches 5-10 min. Place the heel of your operated leg on a small towel roll. Tighten your thigh muscles, trying to fully straighten your knee and touch the bed. Hold knee fully straightened for 5-10 s.		Stretching is held for 12- 15 s Progress from 3 to 5 repetitions.
2b,c. Knee ROM-Stretches (cont.)		
2d. Knee ROM-Stretches (cont.)		

<p>3. From lying near a wall, use a small ball/roll to slide your heel on to the wall, so as to control bending your knee.</p>		<p>Progress from 10-20 repetitions.</p>
<p>4. From lying, with your knee straight, raise your leg from the bed as high as possible.</p>		<p>Knee quadriceps strengthening. Progress from 3 sets of 10 to 5 sets of 10 repetitions. Hold for 3-5 s each time.</p>
<p>5. Place a roll under your operated knee. Raise your heel off the bed. Straighten your knee as much as possible. Ensure you keep the back of your knee on the roll.</p>		
<p>6. While sitting on a chair (1/2m height from floor), tie up the elastic band on the chair and at your ankle. Kick your leg by straightening your knee.</p>		
<p>7. Standing, support your arms on a chair, if needed for first week. The elastic band behind you (height of your waist) and at your ankle. Kick forward by straightening your knee.</p>		
<p>8. Hamstrings strengthening: Now turn your back face to the door and bend your knee against the resistance of the elastic band.</p>		<p>Progress from 3 sets of 10 to 5 sets of 10 repetitions.</p>
<p>9. Lie on your side, straighten your top leg and raise it to 45°. Hold for 5 s.</p>		<p>Abductor strengthening. Progress from 2 sets of 10 to 4 sets of 10 repetitions</p>
<p>10. Get up from a chair and back down.</p>		<p>Progress from 10-20 repetitions. Progress by not using armrest.</p>
<p>11a. With your back supported on the wall, your feet shoulder apart, squat, hold for 5 s and come back up.</p>		<p>Progress from 10-20 repetitions. Progress to single-leg support as indicated in the exercise below.</p>

11b. Likewise before, perform squats on single leg support.		Progress from 10-20 repetitions.
12. Calf raises. Step with your weight distributed evenly over both feet. Hold on to the back of a chair for support.		Progress from 10-20 repetitions. Progress by not using armrest. Progress to single-leg support
13. Walk in place with large amplitude hip and knee flexion and upper limb movements.		Progress from 10-20 repetitions.
14. Climb on a platform of stairs.		Progress from 10 to 30 steps and gradually do not use arm support. Speed as tolerated.
20-30 min walking or stationary cycling.		Progress from 5 to 20 min. Speed as tolerated.
Enhanced sensori-motor exercise therapy programme (only performed by ESMET group): In addition to exercises 2, 5, 6, 10, 11, 12-14 (FET programme) the training programme included the exercise showed below		
1. Side stepping. Step sideways, moving right to left and left to right, at first 2 times in each direction.		Course length progressed from 10 to 20ft. Width and speed of steps progressed as tolerated. No arm support gradually.
2. Braiding activity: Alternate steps front and back cross-over while moving laterally. Repeat 2 times in each direction.	 a)	Course length progressed from 10 to 20ft. Width and speed of steps progressed as tolerated. No arm support gradually.

	 <p>b)</p> <p>c)</p>	
<p>3. Square stepping exercise, change direction backwards and side step to the beginning.</p>		<p>Repeat for 3 times in each direction. Progress to 5.</p>
<p>4. Walk over small obstacles.</p>		<p>Course length progressed from 10 to 20ft. Width and speed of steps progressed as tolerated. No arm support gradually.</p>
<p>5. Stand next to your work surface. Place a foam (or pillow) and balance on two legs, counting up to 20 s.</p>		<p>Repeat 3 times. Progress from double to single-support. Start again on the other foot. Repeat 3 times for each leg.</p>

<p>6. Tandem Walking. Walk forward stepping on a straight line.</p>		<p>Course length progressed from 10 to 20ft. Width and speed of steps progressed as tolerated. No arm support gradually.</p>
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ESMET: Enhanced sensori-motor exercise training; FET: Functional exercise training; rep: repetitions; min: minutes; ft: feet.

8.3.3 Outcome measures

Outcome measures included both performance-based measures as well as PROMs for the assessment of pain and function. To investigate more comprehensively the effects of the two exercise training programmes on patients, a series of secondary outcome measures, some more novel than others, were included (Figure 8.3). The rationale for including the aforementioned battery of outcomes was to show whether potentially measurable functional properties of training (changes in the physical mobility of the replaced knee i.e. performance in the TUG Test or balance control) could be attributed more to neurophysiological (changes in nervous system function) characteristics, or to morphological (changes in knee form and structure), or even to a combination of the two. Potential changes in morphology are due to changes in muscle cross sectional area, whereas changes in position sense, and muscle reactivity would be attributed to neurophysiological changes (Hupperets *et al*, 2009).

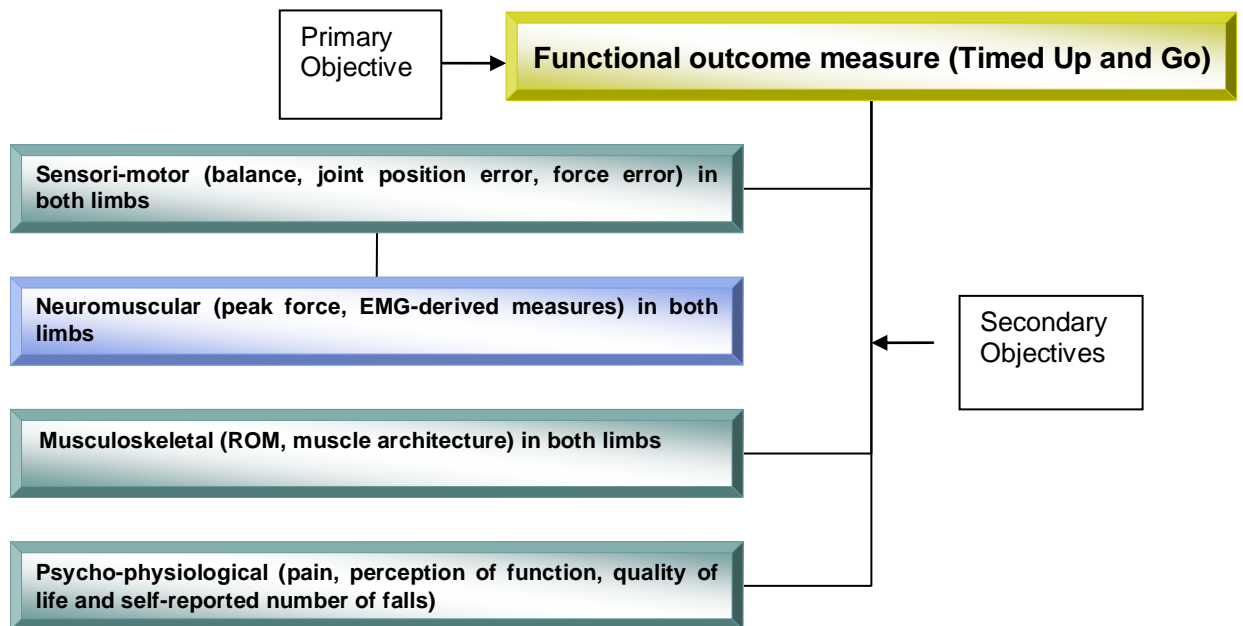
Timed Up and Go Test, balance and joint position error were used as measures of sensori-motor function. Direct (muscle strength) and indirect (EMG-derived measures) measures of neuromuscular performance, as well as measures of muscle size and knee ROM were used to assess the neurophysiological responses to SMT. Self-reported measures of pain, falls' recollection number and Knee Outcome Survey Activities of Daily Living Scale were also used to assess functional mobility and pain levels. Carry-over effects during patients' assessment sessions were minimised by randomly ordering the acquisition of outcomes.

Primary outcome measure

Timed Up and Go Test

The Timed Up and Go Test was selected as the primary outcome measure to assess function, whilst also reflecting patients' capabilities for balance and falls' risk (Minimum detectable change [MDC = 2.49 s]) (Kennedy *et al*, 2005; Shumway-Cook *et al*, 2000; Steffen *et al*, 2002).

Figure 8.3 Diagram showing primary and secondary objectives and outcome measures.

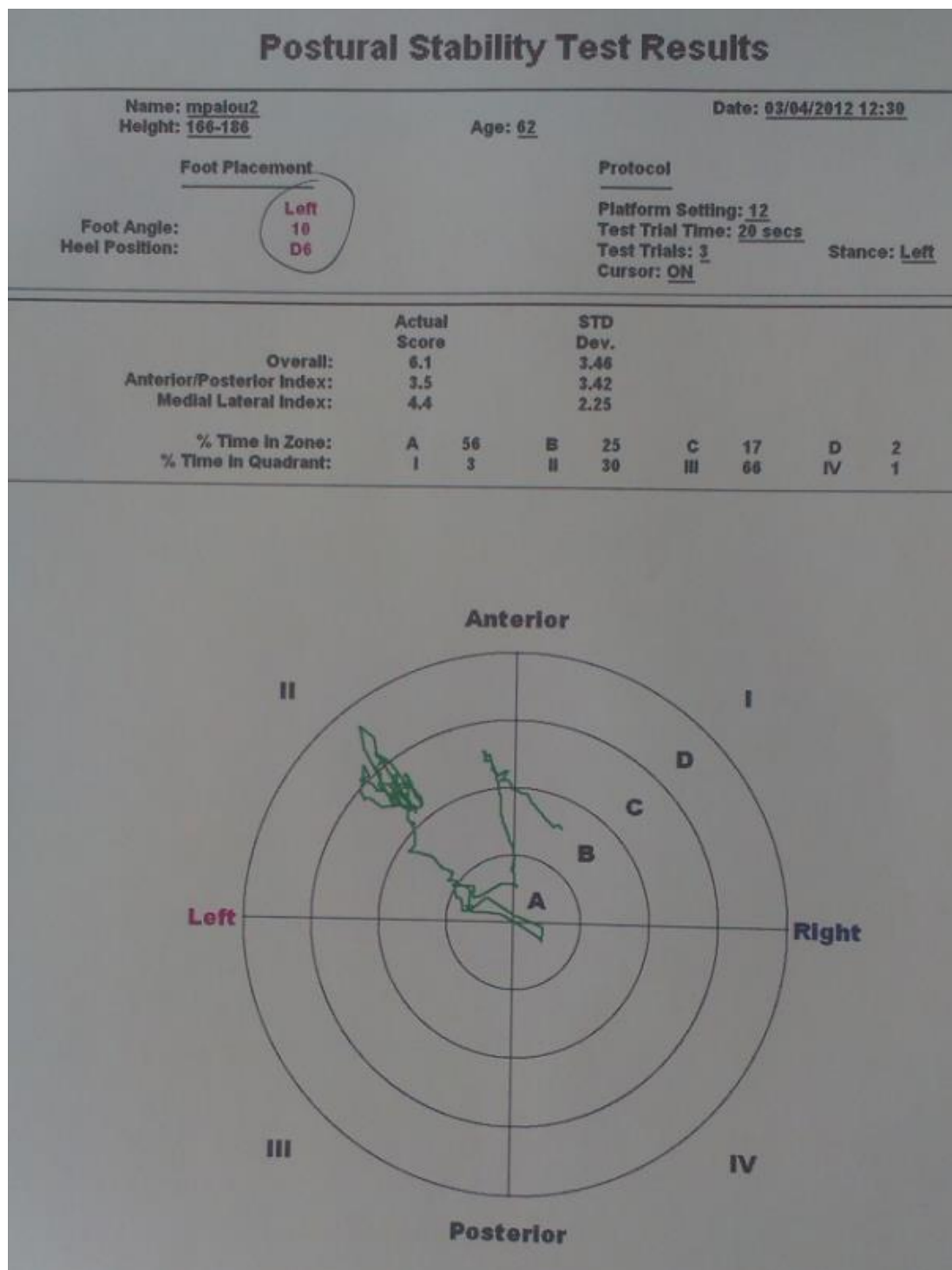


Secondary outcome measures

Balance-related performance indices

Single limb standing balance (for the operated and non-operated leg) was assessed using the protocol described by Cachupe *et al*(2001) and the Biodex Stability System ([BSS] Biodex Medical Systems, Shirley, NY; platform deflection: 12), with feedback limited to an eye-level visual target during concurrent platform tilting over anterior-posterior (AP) and medio-lateral (ML) axes. Examples of patients' balance outcome report sheets is illustrated in Figure 8.4.

Figure 8.4 Postural Stability target: a) patient with impaired balance performance report b) patient with satisfactory balance performance report and c) analytic score report.



Postural Stability Test Results - Bilateral Test

Name: gewrgakopoulou Sm
 Height: 166-186

Age: 76

Date: 04/06/2014 16:19

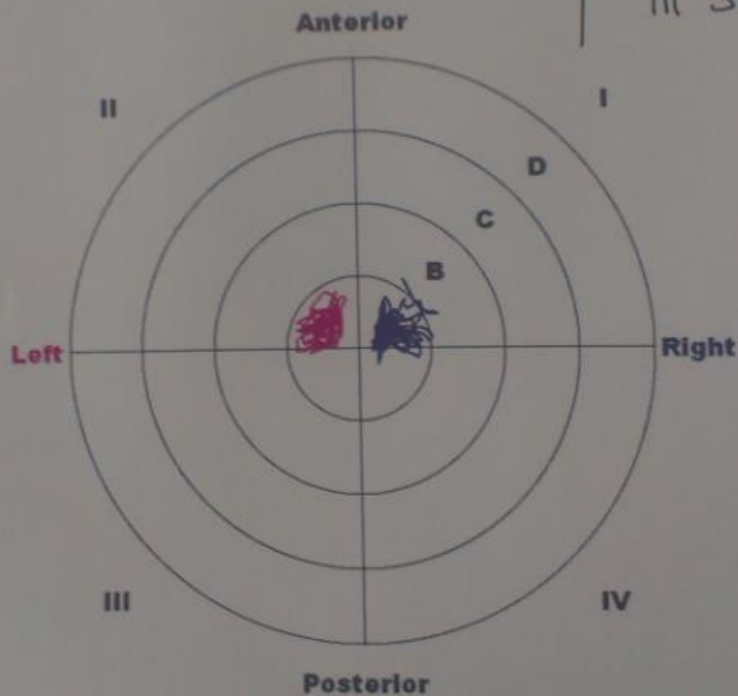
Foot Placement
 Right **Left**
 Foot Angle: 10 10
 Heel Position: D12 D10

Protocol
 Platform Setting: **STATIC**
 Test Trial Time: 15 secs
 Test Trials: 3
 Cursor: ON

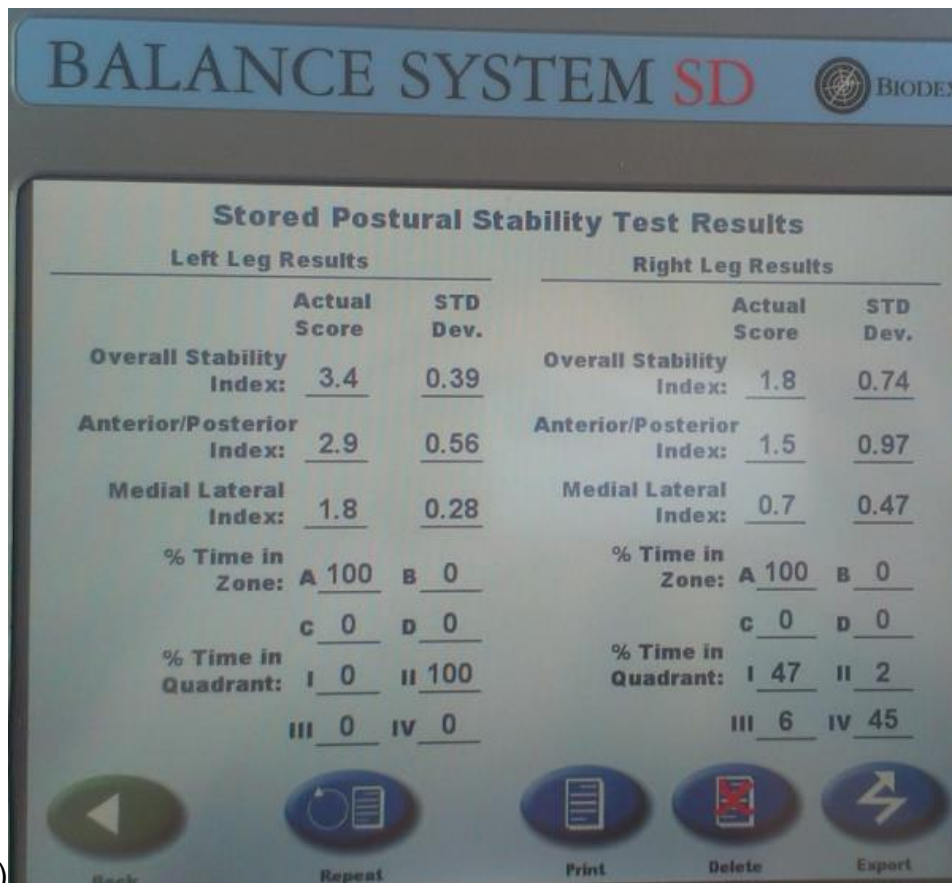
		Right		Left	
	Percent Difference	Actual Score	STD Dev.	Actual Score	STD Dev.
Overall:	3%	2.8	0.88	2.7	0.93
Anterior/Posterior Index:	24%	1.6	1.12	1.2	0.96
Medial Lateral Index:	-10%	2.0	0.79	2.2	0.83

A: 99, B: 1
 I: 35, IV: 65

A: 99
 II 61
 III 39



b)



c)

Sensori-motor performance indices

Sensori-motor performance (SMP) is defined as the ability of a person to scale volitional force precisely (Gillian, 2009). Sensori-motor performance was evaluated by knee joint positional error using a passive-active angle reproduction test (tibial baseline bubble inclinometer [Fabrication Enterprises, Inc., USA]) conducted at 25° and 60° of knee flexion (Gleeson *et al*, 2013; Olsson *et al*, 2004; Peer & Gleeson, 2016). Force error (FE) derived from a SMP task that required the blinded attainment of a target force using the knee extensors, was evaluated. The target force was set at 50 % of PF with the knee in 60° of flexion to reflect what is considered to contribute to peak power outputs from functional neuromuscular performance based on expected power-velocity and force-velocity relationships. The extent of FE indicates the constant error or bias or around a target force meaning that lower scores describe better SMP. Experimentally, the procedure is described by Gleeson *et al* (2008). To evaluate the participants' capacity on SMP performance, FE was calculated as the percentage difference between the target force that had been verbally requested by the assessor during the task and that

produced on the dynamometer by the patient. Absolute values of the estimated errors were used for analysis. For example, in the force perception task, if the verbally requested absolute force measured in Newtons had been 115 N (corresponding to 50 % of the patient's PF), and the actual force produced on the dynamometer by the patient had been 135 N, then the absolute error would have corresponded to 20 N (i.e. 135 N – 115 N), or when expressed as a percentage of the target force (i.e. FE), 17.4 % (i.e. [20 N / 115 N] * 100 %) (Lauzière *et al*, 2012). For any given performance trial, FE was computed using the generic formula:

$$FE = (\text{observed performance value} - \text{target performance value}) / \text{target performance value} \times 100\%.$$

Force error is a novel outcome measure to assess sensori-motor control of TKR patients.

Neuromuscular performance indices

Peak Force (PF)

Muscle strength is reduced following injury and/or surgery and this can be due to arthrogenic inhibition and/or due to limitation of physical activity (Hopkins & Ingersoll, 2000; Rice & McNair, 2010). Not surprisingly, muscle strengthening is an important aspect of TKR rehabilitation, aiming to improve the dynamic stability of the joint system and the body as a whole, and to lessen the potential. and lessen the potential risk of future falls.

To test the knee extensors' PF, measured in Newtons, a dynamometer (Primus RS BTE Dynamometer, The Technology of Human Performance, USA) was used. The description of the procedure is described in Chapter 7 (page 189-0).

The assessment of neuromuscular performance was also indirectly measured for the quadriceps muscle by using electromyography (EMG) equipment. It is well known that during isometric contractions, force and EMG amplitude are well correlated (Basmajian, 1974). Commercially available software (Spike 2 software, version 5.16, Cambridge Electronics Design Ltd., UK) was used for all volitional data capture and interpretation. The description of the procedure is described in Chapter 7 (page 191-2). Normalized values of peak amplitude and RMS were used for

subsequent data analysis. Normalisation of the EMG signal's peak amplitude and RMS (Halaki *et al*, 2012; McKenzie *et al*, 2010) to the baseline MVIC (100%) facilitated inter-group comparisons over time. Reliability and validity of assessing EMG during MVICs has been verified by McKenzie *et al*, (2010).

Musculoskeletal performance indices (Knee ROM and rectus femoris muscle size)

Range of movement (Goniometer)

Range of movement of the knee joint was assessed by goniometry (Jones *et al*, 2003; Edwards *et al*, 2004), and used to quantify the joint's mobility in both groups. Range of movement of both knee flexion and extension were recorded (in degrees) in all assessment sessions for both operated and non-operated knees. Multiple authors have reported the consistency and reliability of ROM measurement for goniometry-derived assessments made within and between testers (ICC = 0.79-0.92) (Edwards, 2004; Gogia 1987; Lavernia 2008; Watkins *et al*, 1991). In a wider context, the examination of knee ROM in patients with knee OA but not yet having undergone surgery, has been shown to offer similarly adequate single-measurement reliability, with ICCs of 0.96 for flexion and 0.81 for extension, respectively (Cibere *et al*, 2004).

For the measurement of active knee flexion and extension, patients were positioned supine lying, with a pillow under their head and were asked to actively flex, and subsequently extend, each of their knees. A universal goniometer was placed on the lateral aspect of the knee with one indicating-arm in line with the lateral malleolus and the other in line with the greater trochanter of the femur. Only a voluntary range was tested. The best of three attempts was recorded.

Assessment of muscle architecture (ultrasound)

The absolute force of a muscle is known to be directly proportional to its cross-sectional area (Weber *et al*, 1846). Quadriceps cross-sectional area have been extensively used in research alongside direct or indirect muscle strength measures (dynamometry or EMG, respectively) to quantify the behavior of muscle size after pain, dysfunction, surgery or pathology (Guo *et al*, 2010; Montes, 2001; Seymour *et al*, 2009). Similarly, muscle strength has been found to be related with limb muscle size as measured by ultrasound imaging (US). Changes in muscle thickness, cross-sectional area (CSA), width and thickness of rectus femoris during isometric and

dynamic contractions have been frequently used to monitor mechanistic changes in functional performance (Montes, 2001; Moreau *et al*, 2009; Seymour *et al*, 2009). Muscles respond to increased changes in activity' level changes, with hypertrophy, and increased capability for force production. Morphological adaptations result from increases in myofibrillar size and number (increase in the synthesis of the contractile proteins actin and myosin within the myofibril and an increase in the number of myofibrils within a muscle fibre). Neurophysiological adaptations result from specificity of training, which encompass learning and coordination. Usually, neurological adaptations make their greatest contribution during the early stages of a training programme, whereas morphological processes commence at a later stage (six weeks) (Folland & Williams, 2007).

It is known that when RF is contracted, there is an increase in its depth and a decrease in its width due to concomitant contraction of the surrounding muscles (Delaney *et al*, 2010). It is important to measure RF both in a relaxed and contracted state, as the contractile ability of a muscle indicates the quality of the contractile material and therefore, of the muscle's functional capability. Changes in muscle strength cannot only be ascribed to changes in muscle size, but also to afferent activity, the number of active cross-bridges producing fibre' tension, remodeling of sarcomeres in parallel and in tension, intra-muscular connective tissue (de Boer *et al*, 2007).

Ultrasound equipment compared to CT and MRI is available and portable in all hospitals and in principle, all trained non-specialists and physiotherapists could perform muscle testing rapidly and cost-effectively using these techniques. Changes in muscle thickness and cross-sectional area (CSA), of the RF during isometric and dynamic contractions have been frequently used (Montes, 2001; Moreau *et al*, 2009; Seymour *et al*, 2009). In this study, CSA of the RF muscle was measured in order to investigate alterations in muscle' strength and size during recovery from surgery. The description of the procedure is described in Chapter 7 (page 192).

Patient-reported measures of psychophysiological performance, functional mobility and pain

Antecedent and contemporary functional balance ability associated with total knee replacement was assessed by patient-reported number of falls experienced in the

first year prior to surgery, and during the follow-up period (surgery to 14 weeks post-surgery). Unfortunately, the patient-reported number of falls experienced was self-reported and based on patients recall capability.

The Short Form-12 (SF-12) (Appendix VIII) and a more specific Knee Osteoarthritis Outcome Score (KOOS) (Appendix VI), have been used as indicators of patients' perceptions regarding function, symptoms and mental status and quality of life (Nilsson *et al*, 2009; Roos, 2003). Self-reported functional mobility was assessed using the Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL) (Appendix VII), with an $MDC_{95\%CI} = 11.4$ scale units, reported (Impellizzari *et al*, 2011).

Pain was assessed by a NPRS consisting of a 10 cm line, with its extremities reflecting semantic opposites (no pain; worst pain imaginable). A more accurate predictor was found by converting the changes on the NPRS to percentages, by Sloman *et al* (2006), who reported an MCID of 28.6 % reduction in pain response [on the NPRS] post-orthopedic surgery.

8.3.4 Orthopedic-related factors and exercise compliance characteristics influencing the main outcomes of knee performance (assessment of potential covariates)

In order to account for the influence of any potential covariates that might need to be controlled within the final analysis investigating the clinical efficacy of FET and ESMET exercise therapy programmes on the primary (TUG) and secondary outcome measures, the potential effects of candidate anthropometric and orthopedic-related factors were considered. This was undertaken when a dependent outcome measure at baseline had been correlated with these candidate covariates. These variables included anthropometric characteristics, such as weight, age, orthopedic related characteristics such as years with a diagnosis of knee OA, time patients were assigned to the waiting list until surgery, and exercise-compliance-related characteristics.

Waiting time for surgery

Evidence has suggested that pain increases and function deteriorates, with longer wait times for surgery (Quintana *et al*, 2006). A wait time exceeding 12 months from

consultation to surgery may adversely affect the 12 month outcomes after TJR (Fortin *et al*, 2002; Quintana *et al*, 2006). Long wait times are not free from adverse effects and have irreversible effects on the results of the therapeutic intervention (Vergara *et al*, 2011). Patients' narratives showed increasing pain and deterioration in function during the journey towards hip replacement and reported to have made essential changes to how they filled their days. They experienced lost and wasted time and faced disruption to the temporal order of their lives. A surgical date marked in the calendar became their focus (Johnson *et al*, 2014). Therefore, wait time to surgery has been deemed as an essential factor for determining successful surgical outcomes (Derret *et al*, 1999; Quintana *et al*, 2006).

Therefore, time (in weeks) that patients were on the waiting list before undergoing surgery, as well as years diagnosed with OA, were recorded and were considered for further analysis.

Compliance with exercise and Volume of exercise performed

Recording patients' structured and unstructured physical activities, and compliance during rehabilitation is essential to assess patients' physical ability, their perceived status and determination during recovery and rehabilitation. Determining the frequency, intensity and duration of exercises during rehabilitation is an important factor for controlling the heterogeneity of exercise dosage. Unfortunately, there is no gold standard for measuring compliance as this feature needs to be defined situationally. Therefore, self-reported weekly frequency and duration of home exercise sessions was monitored with weekly diaries (Figure 8.5). To assess compliance with the home exercise programme and corroborate data within the patients' weekly diaries, patients were required to complete a compliance questionnaire at their 8- and 14-week post-treatment assessments (Figure 8.6). The questionnaire asked the patients to detail how many times they had performed the home exercises in the past week, how long they spent doing the exercises, whether they had stopped doing the exercises and if so when. In addition, the patients were asked whether they felt that their physical activity levels had gone up, stayed the same or gone down in the previous 6-week period. The relevant questionnaire has been previously used in a study by McCarthy *et al*, (2004) who implemented a home-based exercise programme in knee OA patients. Because performance of patients after TKR has been shown to be directly linked with the rehabilitation

programme followed, an appropriate description of how much exercise that the patients had actually accomplished across the entire rehabilitation programme, needs to be taken into consideration as a potential covariate within the analysis.

Figure 8.5 Seven-day recall exercise diary completed weekly during the 12-week exercise programmes.

WEEK 1...12									
Exercise Training programme	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Sets/Repetitions	Amount of time (min)
Ankle ROM									
Knee ROM- Stretches 5-10min									
Heel slide on wall									
Straight leg raise									
Quadriceps sets (short arc)									
Quads strengthening with elastic band (sitting)									
Quads strengthening with elastic band (standing)									
Hamstrings strengthening with elastic band (standing.)									
Abductors (side-lying)									
Sit-to-stand									
Wall slides									
Calf raises									
20-30 min walking or stationary cycling									
Climb on a platform of stairs									
Marching									
Side stepping									
Braiding activity									
Square stepping									
Walk over small obstacles									
Balance on foam									
Tandem Walking									
TOTAL (min)									

Figure 8.6 Exercise compliance questionnaire (adapted from McCarthy *et al*, 2004).

Compliance questionnaire

PLEASE ANSWER THE FOLLOWING QUESTIONS HONESTLY. THE ANSWERS YOU GIVE WILL NOT AFFECT ANY FURTHER TREATMENT YOU MAY RECEIVE.

1. IN THE LAST 6 WEEKS HOW MANY TIMES A WEEK HAVE YOU BEEN DOING THE EXERCISES SHOWN TO YOU BY THE PHYSIOTHERAPIST?

- a. Never.
- b. Once a week.
- c. Twice a week.
- d. Three times a week.
- e. Four times a week.
- f. Five times a week.
- g. Six times a week.
- h. Every day.
- i. Twice a day.

2. WHEN YOU DO YOUR HOME EXERCISES, HOW LONG DO YOU SPEND DOING THEM?

- a. Less than five minutes.
- b. Less than ten minutes.
- c. Less than fifteen minutes.
- d. Less than half an hour.
- e. More than half an hour.

3. IF YOU HAVE STOPPED DOING THE EXERCISES, HOW LONG AGO DID YOU STOP?

- a. I have not stopped.
- b. Less than a week ago.
- c. Less than a month ago.
- d. If more than a month ago please note how many months ago.

4. HAS YOUR PHYSICAL ACTIVITY LEVEL –

- a. Gone Up
- b. Gone Down
- c. Stayed the same

8.4 Data protection

A 'master copy' of individual identification numbers unique to each participant was stored in a safe place on site and was accessible only to the named principal investigator. This identification number corresponded with the participants' personal details and any participant information material and consent forms. This number was

used throughout the research of the study to correspond with any scientific data collected; no personal and identifying information were used. All data was collected by the principal investigator throughout the clinical trial, and access to data was only available to the key researchers and associated collaborators.

All collated data was stored electronically on the designated research laptops hard drive and back-up disc. The laptop and back-up discs were password protected, including the master copy of participants identification numbers (stored in a separate secure location within the Orthopaedic department of the hospital). Any published literature of this clinical trial did not include any identifying information for patients other than basic demographic data e.g. patient's number, age, sex, height etc. Written documentation and data were also stored in a paper format within the participant's medical notes as per normal clinical practice.

The storage and subsequent destruction of data were compliant with the Data Protection Act 1998. Data records will be destroyed after eight years following discharge, as per the health care records policy at University Hospital Rion NHS, Patras, Greece. All forms of data were securely kept in locked cabinets within locked rooms. Only the principal investigator and associated collaborators had the permission to use and access. All collected information during the course of this research was kept strictly confidential and any information that could leave the hospital had patients' names and addresses removed to ensure anonymity.

8.5 Indemnity

Queen Margaret University, Edinburgh, UK was the academic sponsor for this PhD research programme. University Hospital Rion NHS, Patras, Greece Foundation assumed the clinical responsibility for issues arising from the conduct of this research including the clinical supervision of PhD candidates and any harm that might have occurred while they are working with the patients in the specified hospital. Additionally, the latter hospital had taken the responsibility for the patients' welfare in all other aspects of their routine care.

8.6 Statistical Analysis

The effects of enhanced sensori-motor exercise training programme were assessed for each outcome measure using separate factorial ANOVAs involving group

(functional exercise training; enhanced sensori-motor exercise training) by leg (non-operated; operated) by test occasion (pre-surgery [0 weeks]; 8 weeks post-surgery; 14 weeks post-surgery), with repeated measures on the latter two factors. Assumptions underpinning the use of ANOVA were assessed and corrections used (Greenhouse-Geisser [GG]), where appropriate. In the case, where no between-limb differences were found (or, for outcomes that had focused on bilateral limb capabilities, such as the TUG), group (functional exercise training; enhanced sensori-motor exercise training) by test occasion (pre-surgery [0 weeks]; 8 weeks post-surgery; 14 weeks post-surgery) interactions were assessed with repeated measures on the latter factor. In this case, the average of the operated and non-operated limbs data values (combined limbs) were used.

In addition, analyses of covariance (ANCOVA) were used to assess the effects of anthropometric and orthopedic-related factors, when the dependent outcome measures at baseline, were correlated with these factors, on the clinical efficacy of FET and ESMET exercise therapy programmes on primary (TUG) and secondary outcome measures. Each ANCOVA was employed to test null-hypothesis of no difference for outcomes between the group mean responses for the patients in both groups following TKR exercise therapy programmes. Moreover, a relative effect size (ES; Cohen's *d*) was calculated using pooled standard deviations (SD) (Field, 2013). Effect size (ES; Cohen's *d*; *i.e. relative effect size*) was calculated using pooled standard deviations (Field, 2013). The ES therefore represented the magnitude of the differences in outcome measures amongst groups, or in intra-group changes over time, expressed relative to a measure of heterogeneity/homogeneity within the sample's scores (SD), with values of 0.20, 0.50, and over 0.80 representing small, moderate, and large changes, respectively. The a priori experimental design sensitivity had been expected to offer approximately 80 % power statistically for avoiding type-II error in the detection of a moderate relative effect (relative ES of between group differences at 3 months post-TKR = ~0.7) (Mizner et al, 2005a; raw ES: 1.7 s) for the Timed Up and Go Test (30 patients per study group) at the study's primary endpoint (14 weeks post-surgery). Interpretation of findings was based on the indices' clinimetric properties, as discussed in Chapter 3 and Chapter 7. Statistical significance was accepted at $p < 0.05$.

Pearson product-moment correlation coefficients were used to explore:

- i) Correlations that may reflect an interlink between PROMs and indices that measure physical performance (i.e. TUG Test).
- ii) Correlations amongst changes scores of indices of physical, sensori-motor, neuromuscular and muscle size performance.

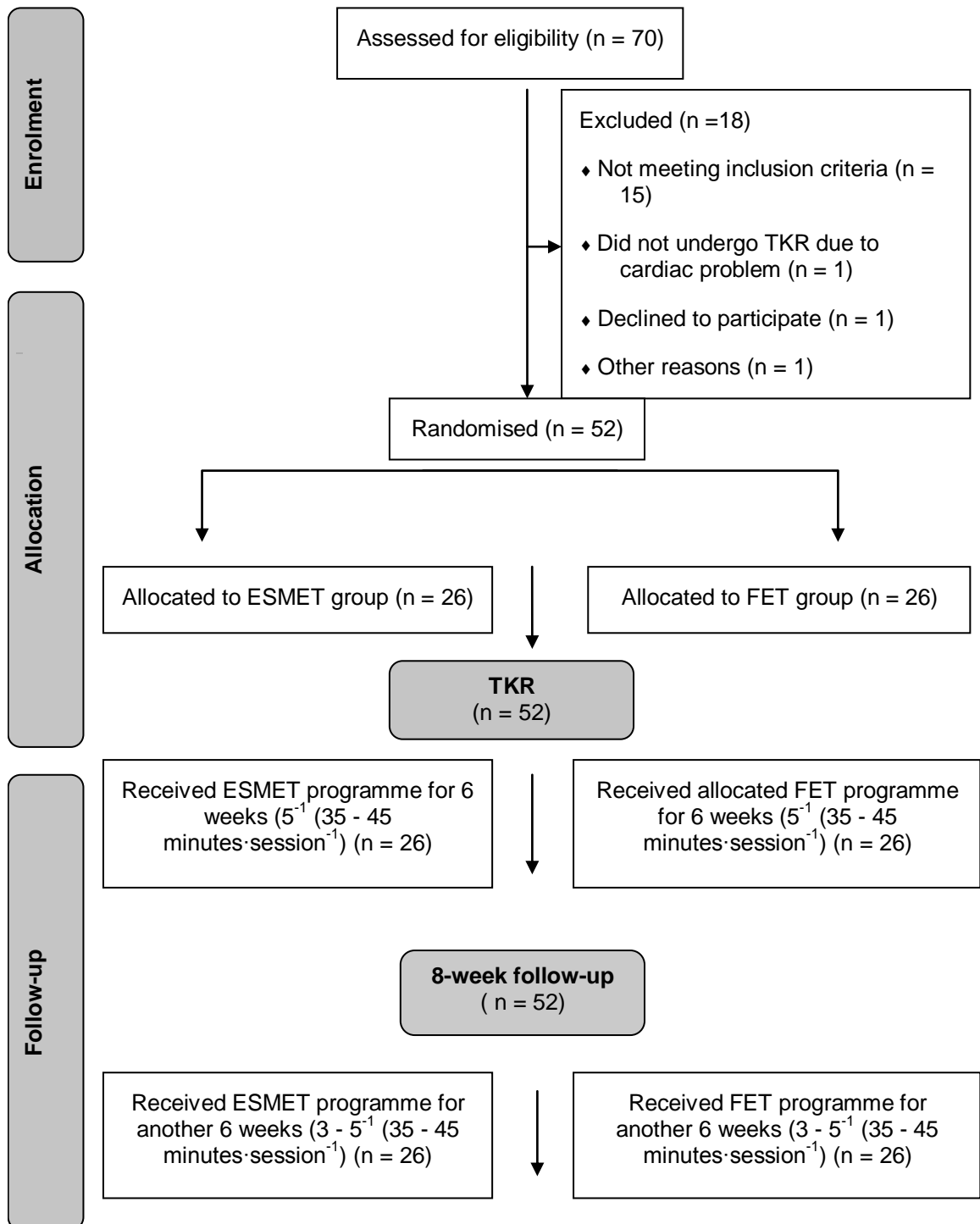
The Pearson product-moment correlation coefficient comprises a quantification of the strength of a linear relation between two variables. It is quantified on a scale that has no units and may embody a value from +1 to -1, in which +1 signifies likely a strong positive correlation, while -1 signifies likely a strong negative association, and 0 signifies no relation between the variables. The correlation coefficients were subjectively interpreted as follows: 0.90–1.0=excellent; 0.70–0.89=good; 0.40–0.69=modest; 0.20–0.39=low; <0.20=slight (Weber & Lamb, 1970). A *priori* alpha levels were set at $p < 0.05$.

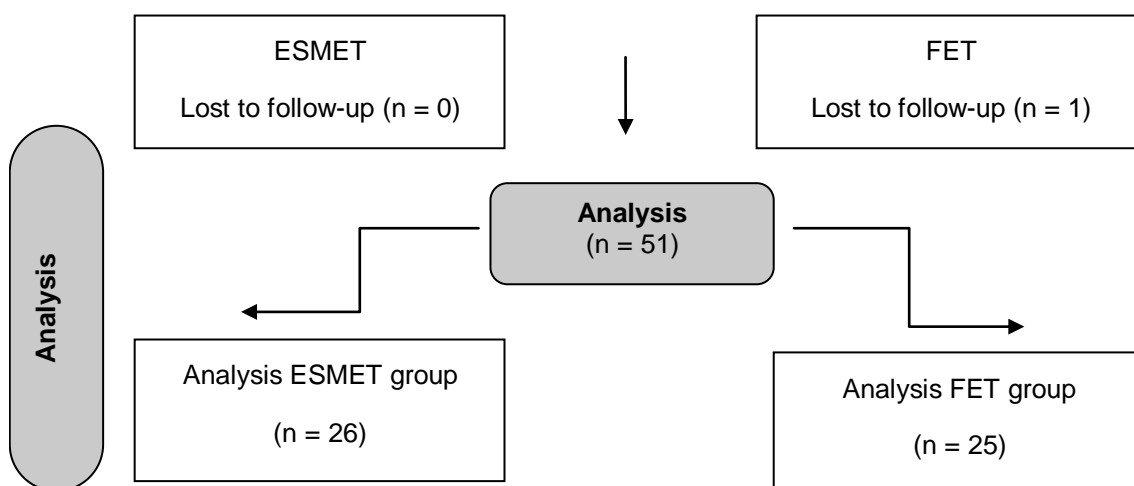
Analyses used the Statistical Package for Social Sciences (SPSS; v. 16.0).

8.7 Results

Figure 8.7 illustrates the CONSORT flow chart detailing recruitment, exclusions, and those patients lost-to-follow-up. A total of fifty-two patients were recruited to the study and allocated to the intervention ($n = 26$) or to the control group ($n = 26$). Demographic and baseline characteristics for the patients are presented in Table 8.3. A total of 51 patients completed all outcome measures at the three assessment occasions (pre-surgery (pre-surgery [0 weeks]; 8 weeks and 14 weeks post-surgery). Due to a mounting financial crisis mounting in Greece, which had been concomitant with the study's delivery, and which curtailed hospital monies available for prostheses and ancillary equipment, the number of TKRs initially expected within the planned time-scale for fulfilling the PhD's programme of research could not be realised. No statistical significant differences were observed between the intervention and control groups on the baseline scores ($p > 0.05$). No adverse events from the interventions were noted.

Figure 8.7 Patient CONSORT flow of the study





TKR: Total knee replacement; ESMET: Enhanced sensori-motor exercise training group; FET: Functional exercise training group.

Assessing the normality of data

Underlying assumptions of normality, (Shapiro-Wilk's test used) and comparisons of the baseline variability characteristics of all outcomes were used to assure homogeneity of variance for data amongst groups (FET; ESMET) are presented in Chapter 7 (Table 7.4, page 197).

Table 8.3 Pre-surgery (baseline) demographic characteristics, time on the waiting list and measures of functional performance and pain.

Variable	Group	N	Mean (SD)	F	p value
Age (years)	ESMET	26	71.5 (5.4)	0.01	0.98
	FET	26	72.9 (5.5)		
Height (m)	ESMET	26	1.68 (0.1)	1.30	0.25
	FET	26	1.62 (0.1)		
Body mass (kg)	ESMET	26	82.5 (11.9)	1.63	0.20
	FET	26	81.9 (8.0)		
Time to surgery (weeks)	ESMET	26	15.3 (12.8)	0.91	0.34
	FET	26	17.2 (14.9)		
Falls (No. of falls during one year pre-surgery)	ESMET	26	1.9 (0.6)	3.46	0.07
	FET	26	2.4 (0.8)		
TUG (s)	ESMET	26	15.9 (3.6)	0.34	0.56
	FET	26	16.9 (3.8)		
NPRS (cm)	ESMET	26	6.7 (1.2)	0.02	0.88
	FET	26	7.0 (1.1)		

ESMET: Enhanced sensori-motor exercise training; FET: Functional exercise training; TUG: Timed Up and Go; NPRS Numeric Pain Rating Scale; No.: Number; $p < 0.05$.

As measured with weekly diaries, patients' self-reported overall time-spent in exercising was described as shown in Table 8.4.

The overall time-spent in exercising ($\text{Exercise}_{\text{OV. TIME}}$) that the training groups performed for each of the six weeks of training period was computed by the following formula (measured in min):

$$\text{Exercise}_{\text{OV. TIME}} = (\text{Frequency of sessions per week} * \text{time spent on each session}) * 6$$

For exercise compliance characteristics (self-reported volume of exercise), a statistical significance between groups was revealed, with the ESMET group presenting with higher levels of variance compared to the FET group. Although statistical significance ($p < 0.01$) was revealed, with the ESMET group presenting with higher levels of variance compared to the FET group, the magnitude of differences in volume of exercise training between groups was considered clinically minimal (10.3 % difference between groups, favouring ESMET). It had been hypothesised that overall time spent in exercise might have differentially influenced the performance of the ESMET and FET groups on primary and secondary outcomes due to its potential to act as a conditioning stimulus for physical performance capacities. However, there was neither significant correlation amongst overall time spent in exercising and outcomes of function (PROMs and objectively-measured) or physical performance capacities (with the exception of PF at baseline [weak correlation, $r = 0.4$; $p < 0.01$]), nor as noted previously, was there significant differences in overall time spent in exercise at baseline between ESMET and FET groups. As such, overall time spent in exercise, was not considered as a candidate covariate for group mean comparisons using ANCOVA.

Table 8.4 Self-reported overall time spent in exercise factors of each training group throughout the rehabilitation period. Data are mean (SD).

Group	First 6 weeks of training		Final 6 weeks of training	
	Frequency of sessions per week.	Time spent on each session (min).	Frequency of sessions per week.	Time spent on each session (min).
FET	4.3 (0.7)	33.8 (3.9)	2.9 (0.3)	38.6 (3.7)
ESMET	4.8 (0.4)	34.6 (4.7)	2.9 (0.4)	41.7 (4.5)

ESMET: enhanced sensori-motor exercise training; FET: Functional exercise training; SD: standard deviation.

The ESMET group presented with an exercise compliance of ~83 % per week while the FET group with an exercise compliance of ~72 % per week for the 12 weeks of the exercise programme. According to this formula, the ESMET group presented with a difference of ~20min per week (166.1 min vs 145.3 min) for the first six weeks and a difference of ~9min per week (120.9 min vs 111.9min) for the final six weeks.

As it would be expected, due to the deconditioning of the knee selected for surgery, baseline differences were found between operated and the non-operated limbs (acting as control), which had been examined by paired t-tests. The non-operated limb exhibited greater performance in balance control (~18 % difference; $p < 0.05$), better sensori-motor performance (15 - 18 % difference; $p < 0.01$), better neuromuscular performance (10 - 25 % difference; $p < 0.001$) and better musculoskeletal performance (~12 % difference; $p < 0.001$) compared to the operated limb.

8.7.1 Changes in primary and secondary outcome measures

Table 8.5 displays the changes in outcome measures from baseline (pre-surgery) to mid-way (8 weeks) and to the end of the exercise programmes (14 weeks) post-surgery, respectively. The ESMET group experienced statistically significant improvements at the end of training that were superior in comparison to the control group for most outcomes ($p < 0.005$).

Table 8.5 Group mean scores for functional, sensori-motor and balance performance at pre-surgery and at 8 weeks and 14 weeks post-surgery.

Variable Mean (SD)	Group Mean (SD)	Pre-surgery Mean (SD)	8 weeks Mean (SD)	14 weeks Mean (SD)	F	ES	% change
TUG (s)	ESMET	15.8 (3.5)	11.2 (2.9)	8.1 (1.7)	0.002	11.2	2.8
	FET	17.0 (3.7)	15.1 (3.8)	12.4 (2.5)			1.4
OSI (degrees)	ESMET	3.8 (1.3)	2.7 (0.9)	1.9 (0.6)	0.001	24.8	1.3
	FET	3.4 (1.7)	3.3 (1.4)	3.0 (1.2)			0.3
APSI (degrees)	ESMET	3.0 (1.4)	2.0 (0.8)	1.5 (0.7)	0.001	16.2	1.4
	FET	2.2 (1.1)	2.0 (0.6)	2.1 (1.0)			0.1
MLSI (degrees)	ESMET	2.1 (1.0)	1.5 (0.6)	1.0 (0.5)	0.001	21.6	1.3
	FET	2.0 (1.3)	1.4 (0.6)	2.0 (0.9)			0.0
JPE₆₀ (%)	ESMET	16.3 (6.1)	7.1 (4.1)	5.2 (2.6)	0.001	9.6	1.8
	FET	17.1 (9.6)	13.9 (6.6)	12.8 (5.9)			0.4
FE(%)	ESMET	19.9 (15.7)	11.9 (9.8)	9.2 (8.5)	0.003	6.2	0.7
	FET	19.3 (13.7)	22.5 (18.5)	20.8(15.6)			0.0

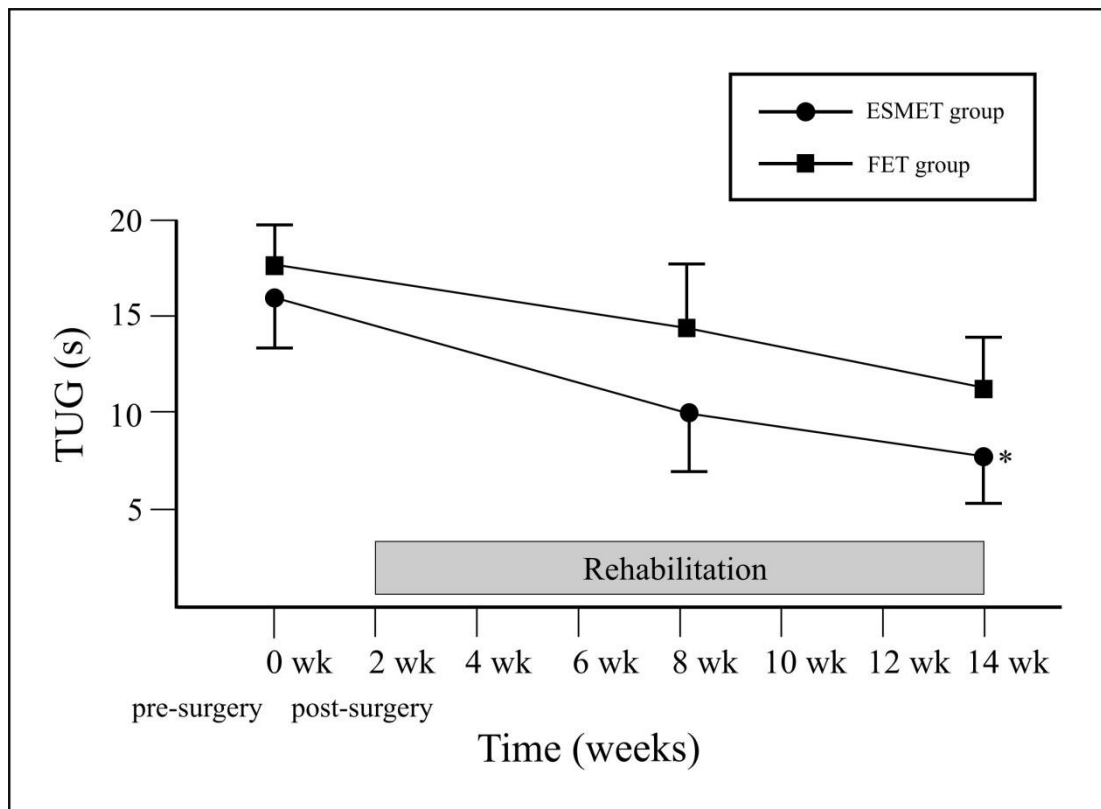
ESMET: Enhanced sensori-motor exercise training group; FET: Functional exercise training group; TUG: Timed Up and Go Test; OSI: Overall Stability Index; AP: Antero-posterior index; ML: Medio-lateral index; JPE: Joint Position Error; p value signifies the statistical significance of the differences between the groups; For OSI, APSI, MLSI, JPE₆₀ and FE average values of operated and non-operated limbs (combined limbs) are presented. ES: relative effect size, computed as (group mean score at 14 weeks – group mean score at pre-surgery) / pooled SD.

Changes in Timed Up and Go Test (Primary objective outcome measure)

The ESMET group showed significantly greater reductions in the time taken to complete TUG Test (7.8 ± 2.9 s) compared to the FET group (4.6 ± 2.5 s) over the training period [$F_{(1.7,82.5)GG} = 11.2$; $p < 0.005$] (~20 % difference) (Figure 8.8). Table 8.5 shows group mean scores for experimental and control groups at baseline, 8-weeks post surgery, and 14-weeks post surgery. Comparisons using a priori orthogonal difference contrasts suggested that the superior gains made by the ESMET group for the TUG Test were elicited progressively over the period of training, with gains elicited between baseline and 8-weeks post surgery (29.1 %) and between 8 and 14 weeks post surgery (34.2 %). These were similar in magnitude, but significantly greater than control ($F_{(1,49)} > 11.1$; $p < 0.001$; Table 8.5).

As such, the latter findings suggest that gains in functional performance capabilities as measured by the TUG Test, occurred progressively over the 12 weeks of rehabilitation and that there would be no particular advantages associated with efficacy or logistics, in a cessation of conditioning before the scheduled end of rehabilitation for either the ESMET or FET programmes.

Figure 8.8 Timed Up and Go Test for enhanced sensori-motor and functional exercise training groups from pre-surgery (0 weeks) to 8 weeks and 14 weeks post-surgery.



TUG: Timed Up and Go; ESMET: enhanced sensori-motor exercise training; FET: functional exercise training. wk: weeks. Data are mean \pm 1SD for the two groups. *significant interaction effects $p < 0.05$.

The relative effect size for group mean change scores of the TUG Test suggested that ESMET elicited more improvement than the FET, with a large effect size (2.8 vs 1.4, respectively).

Changes in secondary outcome measures

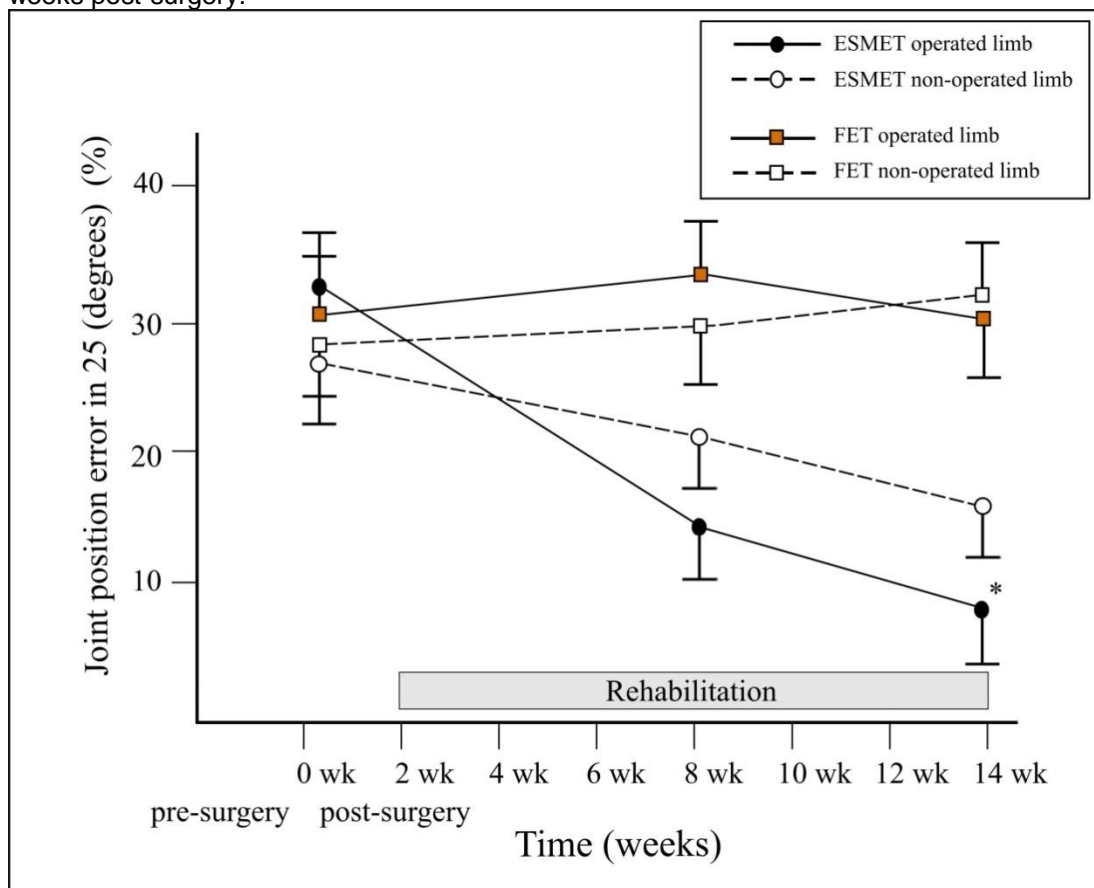
Balance-related performance indices

Balance-related performance was similarly amplified by undertaking enhanced sensori-motor exercise training (~40 % greater improvement compared to the control group; $F_{(2,98)} = 24.8$; $p < 0.001$; Table 8.5). The relative effect size for group mean change scores of the OSI index suggested that ESMET showed more improvement ($d = 1.3$) than FET ($d = 0.3$). Accordingly, a greater rate of gain for the ESMET group was shown for the AP ($F_{(1.5,74.1)GG} = 16.2$; $p < 0.001$) and ML balance indexes ($F_{(1.7,86.1)GG} = 21.6$; $p < 0.001$). Improvements were equivalent for the leg

undergoing surgery and for the contralateral control leg. *Sensori-motor performance indices*

Improvements in JPE were similarly superior for the group undertaking enhanced sensori-motor exercise training for both target angles (25 ° and 60 °), with a relatively greater improvement noted for the leg undergoing surgery (compared to the non-operated leg) when assessed at a target angle of 25 ° of knee flexion ($F_{(1.4, 70.6)GG} = 4.3$; $p < 0.05$, Figure 8.9), but not at 60 ° ($F_{(1.6, 79.4)GG} = 9.6$; $p < 0.001$; Table 8.5). The relative effect size for group mean change scores of JPE suggested that ESMET showed more improvement ($d = 1.8$) than FET ($d = 0.4$).

Figure 8.9 JPE (%) for the 25 ° target angle of enhanced sensori-motor and functional groups for both the operated and non-operated legs from pre-surgery (0 weeks) to 8 weeks and 14 weeks post-surgery.



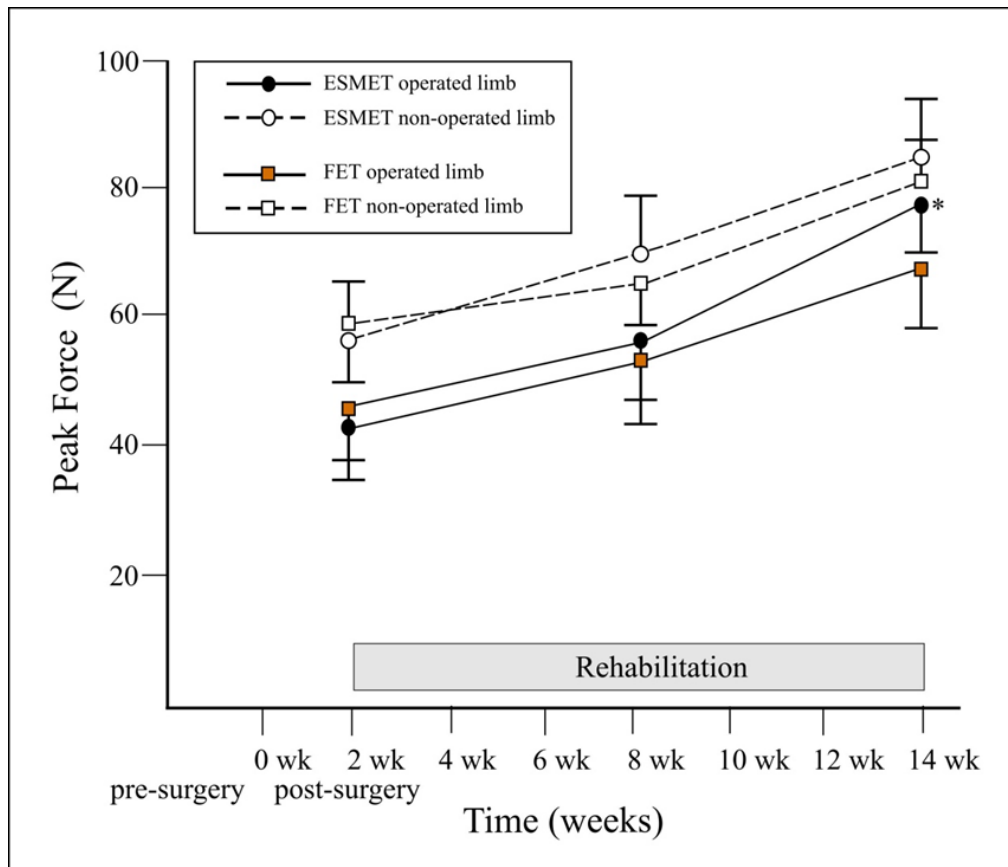
ESMET: Enhanced sensori-motor exercise training group; FET: Functional exercise training group; JPE: Joint Position Error; wk: weeks. Data represent mean \pm 1SD; *significant interaction effects (time x group x limb) $p < 0.05$.

Similarly, improvements in FE were superior for the group undertaking enhanced sensori-motor exercise training over time ($F_{(2,98)} = 6.2$; $p < 0.005$) (Table 8.5). The results suggested that findings were equivalent amongst limbs. The results revealed that in both groups, patients tended to score below the force' target.

Neuromuscular performance

Quadriceps muscle strength as reflected by PF, was amplified by undertaking enhanced sensori-motor exercise training (~27 % greater improvement compared to the effects of the training undertaken by the control group ($F_{(2, 98)} = 7.15$; $p = 0.001$) (Table 8.6). Improvements were equivalent for the leg undergoing surgery and for the contralateral control leg (Figure 8.10) (as appears in Table 8.6, group x time x limb interaction was not statistically significant, but group x time interaction was statistically significant). The relative effect size for group mean change scores for PF confirmed that ESMET showed more improvement ($d = 1.5$) than FET ($d = 0.7$).

Figure 8.10 Peak force scores of enhanced sensori-motor and functional exercise training groups for both the operated and non-operated legs from pre-surgery (0 weeks), 8 weeks and 14 weeks post-surgery, during TKR rehabilitation.



TKR: total knee replacement; ESMET: enhanced sensori-motor exercise training group (intervention); FET: functional exercise training group (control). Data represent mean \pm 1SD; * significant interaction effects (time x group) $p < 0.05$.

Improvements in EMG-derived indices (peak amplitude and RMS) were similarly superior for the group undertaking enhanced sensori-motor exercise training, with a

relatively greater improvement noted for the leg undergoing surgery (~65 % greater improvement compared to control; peak amplitude: $F_{(1.7,85.6)GG} = 36.2$; $p < 0.001$; RMS: $F_{(2, 98)} = 6.9$; $p < 0.005$) (Table 8.6). No significant difference was revealed for the power spectrum frequency parameter ($F_{(1.6,79.6)GG} = 0.52$; ns) amongst groups over time.

Table 8.6 Group mean scores for the patients' objective measures of neuromuscular performance for the ESMET and the FET groups, and for the operated and non-operated limbs.

	Variable		Group	Pre-surgery	8 weeks	14 weeks				
	Limb			Mean (SD)	Mean (SD)	Mean (SD)	F	p value	ES	%
Neuromuscular	iPeak Amp. (%)	op.	FET	100.0 (-)	108.8 (117.6)	126.3 (105.8)			-	26
		non-op.		100.0 (-)	108.2 (77.2)	125.0 (63.6)			-	25
	iPeak Amp. (%)	op.	ESMET	100.0 (-)	153.7 (160.8)	288.1 (109.4)	9.3	0.001**	-	188
		non-op.		100.0 (-)	131.3 (88.4)	156.7 (92.3)			-	57
	iRMS (%)	op.	FET	100.0 (-)	143.7 (148.9)	181.2 (191.4)			-	81
		non-op.		100.0 (-)	130.0 (92.3)	155.0 (169.2)			-	55
	iRMS (%)	op.	ESMET	100.0 (-)	211.7 (141.0)	323.5 (157.1)	3.6	0.005*	-	223
		non-op.		100.0 (-)	144.0 (160.0)	168.0 (136.1)			-	68
	PF (N)	op.	FET	41.8 (17.8)	46.6 (18.6)	55.4 (23.5)			0.8	33
		non-op.		57.2 (16.3)	60.0 (19.3)	69.1 (24.4)			0.7	21
	PF (N)	op.	ESMET	39.8 (15.3)	49.3 (18.0)	67.5 (17.4)	1.3	0.47	1.8	28
		non-op.		55.3 (20.6)	64.7 (24.4)	78.5 (20.9)			1.1	42

ESMET: Enhanced sensori-motor exercise training group; FET: Functional exercise training group; p value signifies the statistical significance of the main effect between the groups; ES: relative effect size, computed as (group mean score at 14 weeks – group mean score at pre-surgery) / pooled SD; iP.Amp.: integrated EMG peak amplitude; iRMS: integrated Root Mean Square; * $p < 0.05$; ** $p < 0.001$; ns: non-significant.

Table 8.7a Group mean scores for the patients' objective measures of rectus femoris muscle size performance for the ESMET and the FET groups, and for the operated and non-operated limbs.

	Variable		Group	Pre-surgery	8 weeks	14 weeks				
	Limb			Mean (SD)	Mean (SD)	Mean (SD)	F	p value	ES	%
Musculoskeletal	ROM Flex (°) op.		FET	106.9 (9.2)	101.3 (6.6)	103.7 (6.9)	1.3	0.34	-	-2.9
	non-op.			113.5 (10.5)	112.5 (9.0)	112.1 (8.5)			-	-1.4
	ROM Flex (°) op.		ESMET	105.1 (10.1)	104.4 (6.9)	107.3 (6.9)			0.02	2.1
	non-op.			114.1 (9.8)	114.6 (9.0)	115.3 (8.8)			0.01	1.0
	ROM Ext (°) op.		FET	-6.9 (5.2)	-4.2 (2.7)	-1.6 (0.9)			1.0	77
	non-op.			-4.3 (4.1)	-3.1 (3.3)	-2.3 (1.5)			0.5	46
	ROM Ext (°) op.		ESMET	-6.0 (4.1)	-2.7 (2.1)	0.2 (1.1)	0.7	0.52	1.4	97
	non-op.			-2.3 (2.4)	-1.5 (1.8)	-0.7 (1.5)			0.6	68

ESMET: Enhanced sensori-motor exercise training group; FET: Functional exercise training group; p value signifies the statistical significance of the main effect between the groups; ES: relative effect size, computed as (group mean score at 14 weeks – group mean score at pre-surgery) / pooled SD; ROM Ext: range of motion in extension; hypoextension = negative (-); hyperextension = positive; * $p < 0.05$; ** $p < 0.001$.

Table 8.7b Group mean scores for the patients' objective measures of muscle size performance for the ESMET and the FET groups, and for the operated and non-operated limbs.

	Variable	Group	Pre-surgery	8 weeks	14 weeks				
	Limb		Mean (SD)	Mean (SD)	Mean (SD)	F	p value	ES	%
Musculoskeletal	CSA _{REL} (mm ²) op.	FET	422.1 (72.0)	497.8 (69.4)	564.0 (91.1)			2.0	34
	non-op.		460.9 (71.4)	537.3 (78.0)	612.1 (98.7)			2.1	33
	CSA _{REL} (mm ²) op.	ESMET	450.2 (69.6)	557.9 (77.4)	708.6 (111.2)	19.6	0.001**	3.7	57
	non-op.		487.4 (64.1)	578.5 (73.9)	663.9 (73.7)			2.7	36
	CSA _{CONTR} (mm ²) op.	FET	338.1 (69.2)	433.0 (85.3)	494.8 (90.7)			2.3	46
	non-op.		371.1 (66.9)	478.1 (80.4)	550.2 (94.9)			2.7	48
	CSA _{CONTR} (mm ²) op.	ESMET	343.1 (67.8)	463.4 (86.9)	595.1 (128.4)	11.3	0.001**	3.7	73
	non-op.		401.2 (65.3)	496.7 (84.6.)	576.3 (81.4)			2.7	44

ESMET: Enhanced sensori-motor exercise training group; FET: Functional exercise training group; p value signifies the statistical significance of the main effect between the groups; ES: relative effect size, computed as (group mean score at 14 weeks – group mean score at pre-surgery) / pooled SD; CSAREL: Cross-sectional area in rectus femoris in relaxation; CSA_{CONTR}: Cross-sectional area of rectus femoris in contraction; * p < 0.05; ** p < 0.001.

Musculoskeletal performance indices (Knee ROM and rectus femoris muscle size)

Results using ANOVA (group x time interaction) identified that ESMET and FET groups had shown similar patterns of improvement over time on ROM during knee extension manoeuvres ($F_{(1.3, 66.8)GG} = 0.65$; ns). However, a greater rate of gain over time for the ESMET group was shown for the knee flexion ROM (~3.5 % greater improvement compared to control; $F_{(1.2, 61.2)GG} = 5.6$; $p < 0.005$). Improvements were equivalent for the leg undergoing surgery and for the contralateral control leg.

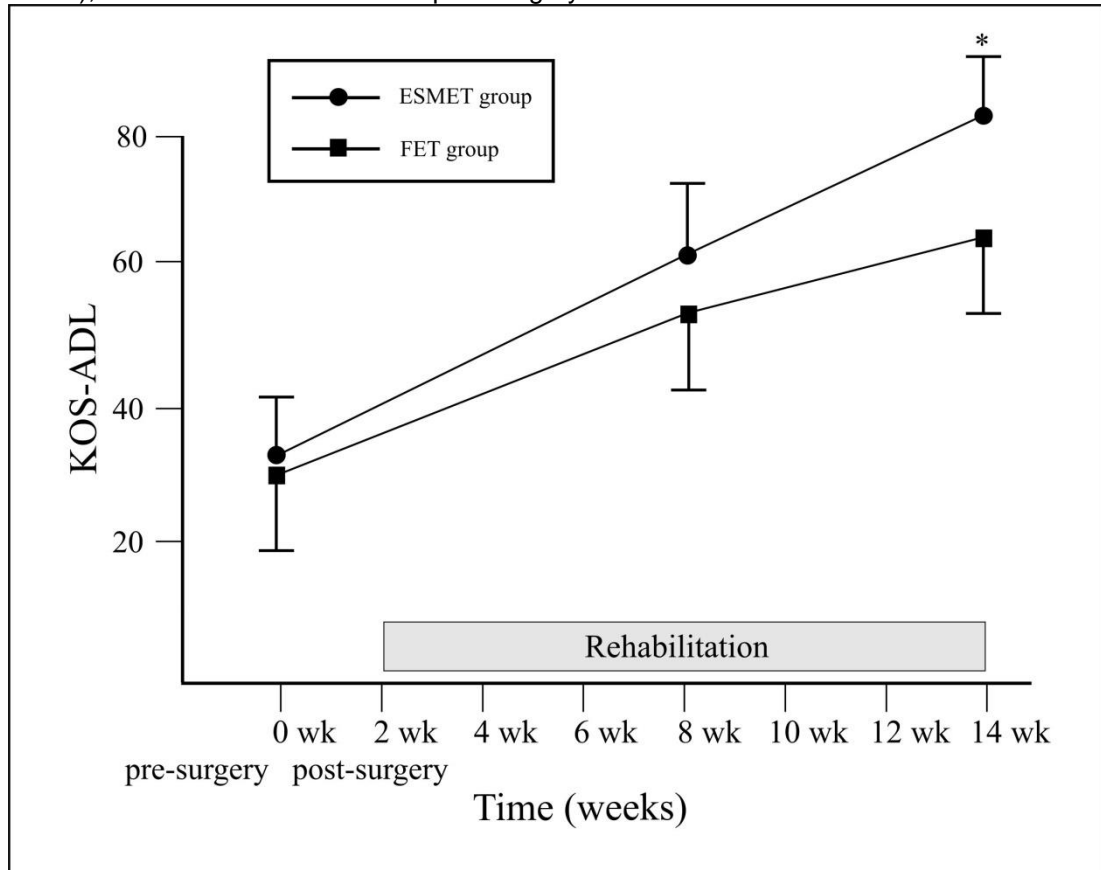
Accordingly, improvements in RF muscle CSA for both the relaxed and contracted (during isometric contraction in 60 degrees of flexion) state were superior for the group undertaking enhanced sensori-motor exercise training, with a relatively greater improvement noted for the leg undergoing surgery (23 % and 27 % greater improvement respectively, compared to control; $CSA_{REL}: F_{(1.6, 82.2)GG} = 19.6$, $p < 0.001$; $CSA_{CONTR.}: F_{(2, 98)} = 11.3$; $p < 0.001$) (Table 8.7).

The relative effect size from pre-surgery to 14 weeks post-surgery for the RF muscle CSA (operated limb) in the contracted state, showed larger improvements ($CSA_{CONTR.}: d = 3.7$) of rectus femoris for the ESMET compared to the FET group ($CSA_{CONTR.}: d = 2.3$), respectively.

Changes in PROMs of functional mobility, psycho-physiological performance and pain levels

The superior gains for ESMET (compared to control) were ~50 % for self-reported performance scores (Knee Outcome Survey Activities of Daily Living Scale ($F_{(1.7, 85.0)GG} = 19.0$; $p < 0.001$) (Figure 8.11). Similar patterns of improved gains were shown for the for pain ($F_{(2, 98)} = 7.02$; $p < 0.001$).

Figure 8.11 KOS-ADL for enhanced sensori-motor and functional groups from pre-surgery (0 weeks), and 8 weeks and 14 weeks post-surgery.

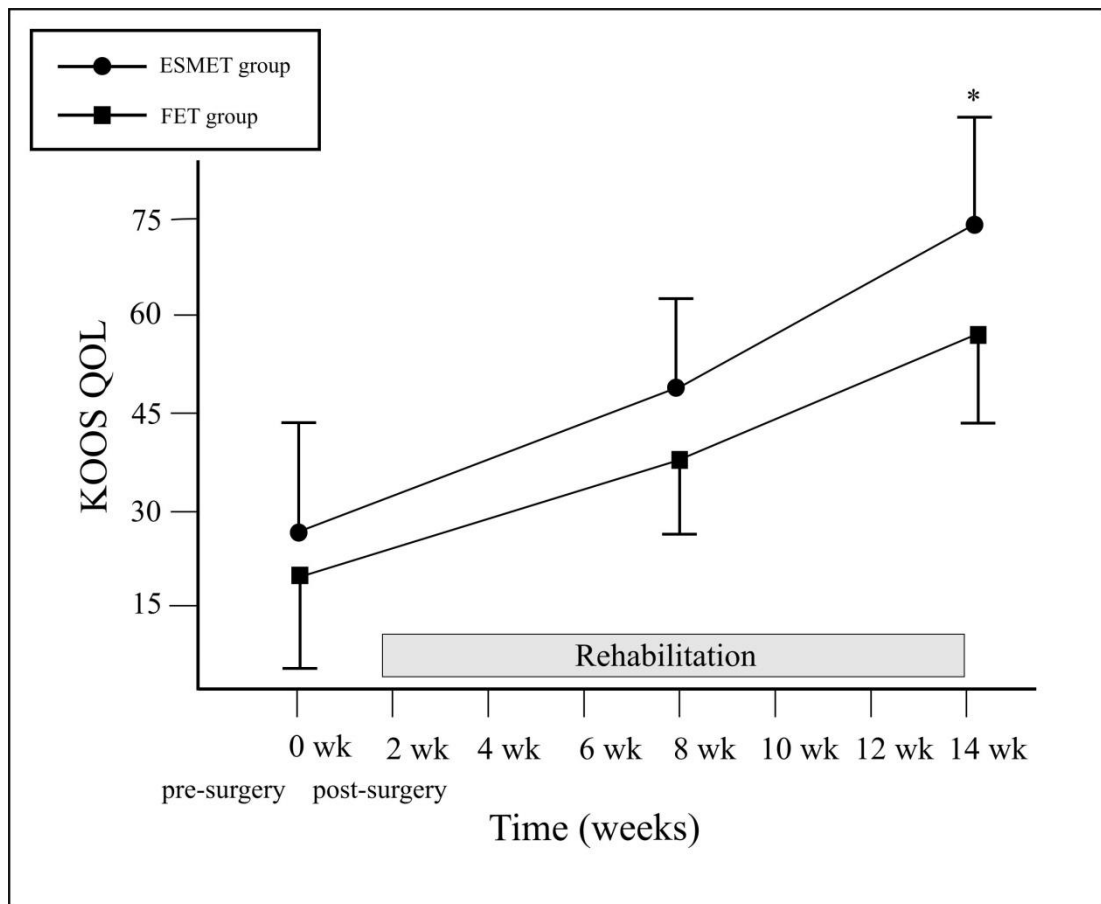


KOS-ADL: Knee Outcome Survey-Activities of Daily Living; ESMET: Enhanced sensori-motor exercise training group; FET: Functional exercise training group; TKR: total knee replacement; wk: weeks. Data represent mean \pm 1SD; * significant interaction effects $p < 0.05$.

The superior gains for ESMET (compared to control) ranged between approximately 25 % - 80 % for self-reported functional performance scores (KOOS [P] ($F_{(2, 98)} = 20.9$; $p < 0.001$), KOOS [S] ($F_{(2, 98)} = 19.2$; $p < 0.001$), KOOS [F] ($F_{(1.5, 77.8)GG} = 13.6$; $p < 0.001$), KOOS [SP] ($F_{(1.7, 85.7)} = 21.0$; $p < 0.001$) and KOOS [QOL] ($F_{(2, 98)} = 21.3$; $p < 0.001$) (Figure 8.12). Similar patterns of improved gains were shown for the SF-12 [physical] ($F_{(2, 98)} = 6.0$; $p < 0.005$) and [mental] components ($F_{(1.8, 87.0)GG} = 3.5$; $p < 0.05$).

The relative effect size elicited by the enhanced sensori-motor training group over the functional exercise training group was large for both SF-12 [physical] and SF-12 [mental] components ($d = 4.8$ and $d = 2.1$, respectively).

Figure 8.12 KOOS-QoL of enhanced sensori-motor and functional groups at pre-surgery (0 weeks), 8 weeks and 14 weeks post-surgery, during TKR rehabilitation.



KOOS QoL: Knee Injury and osteoarthritis outcome Score- Quality of life; ESMET: enhanced sensori-motor exercise training group (intervention); FET: functional exercise training group (control); Data represent mean \pm 1SD; * significant interaction effects $p < 0.05$.

Patients in the ESMET group (5.9 ± 1.3) showed greater improvement in change scores compared to the FET group (4.6 ± 1.0) in pain levels over time ($F_{(2, 98)} = 7.0$; $p < 0.001$) (Table 8.8). The relative effect size for group mean change scores of the NPRS over the period of rehabilitation suggested that ESMET elicited more improvement ($d = 5.5$) than FET ($d = 4.2$).

Table 8.8 Group mean scores for PROMs of pain (NPRS), function (KOOS& KOS-ADL) and quality of life (SF-12), in both training groups, at all assessment occasions (pre-surgery (0 weeks), and at 8 weeks and 14 weeks post-surgery).

Group		Pre-surgery	8 weeks	14 weeks	p value	ES	%
		Mean (SD)	Mean (SD)	Mean (SD)			
NPRS (cm)	ESMET	6.7 (1.1)	3.0 (1.3)	0.7 (0.7)	0.001**	6.5	90
	FET	7.0 (1.1)	4.1 (1.4)	2.4 (0.8)			
KOS-ADL	ESMET	35.4 (6.9)	56.2 (11.4)	79.6 (9.0)	0.001**	5.5	125
	FET	34.0 (7.3)	50.3 (9.4)	60.6 (9.3)			
KOOS[P]	ESMET	38.3 (6.9)	55.3 (13.3)	81.2 (9.5)	0.001**	6.2	112
	FET	35.8(9.9)	41.8 (9.2)	58.5 (8.8)			
KOOS[S]	ESMET	40.6 (10.0)	56.2 (12.2)	78.5 (8.0)	0.001**	3.8	93
	FET	37.0 (13.7)	43.2 (12.9)	54.7 (10.3)			
KOOS[ADL]	ESMET	41.2 (10.0)	54.8 (16.7)	81.5 (11.9)	0.001**	4.0	98
	FET	37.9 (11.4)	43.2 (9.6)	58.8 (10.1)			
KOOS[SP]	ESMET	19.8 (8.7)	27.1 (12.8)	55.6 (13.6)	0.001**	4.1	180
	FET	14.3 (8.7)	15.4 (10.7)	28.7 (13.5)			
KOOS[QoL]	ESMET	27.9(9.1)	43.0 (11.7)	72.3 (9.8)	0.001**	4.9	159
	FET	25.9 (11.6)	29.6 (10.8)	48.9 (10.5)			
SF-12 _[Physical]	ESMET	31.7(3.4)	41.1 (4.5)	47.9 (4.2)	0.004*	4.8	51
	FET	32.1(4.4)	36.3 (7.2)	43.9(7.8)			
SF-12 _[Mental]	ESMET	41.2(5.5)	46.6 (4.2)	53.0 (3.3)	0.04*	2.1	29
	FET	40.6(6.6)	43.7 (6.1)	47.4(6.2)			

NPRS: Numeric pain rating scale; KOS-ADL: Knee Outcome score-Activities of daily living; KOOS: Knee Oxford Osteoarthritis Score; P: Pain; S: Symptoms; SP: Sports and recreations; SF-12 Short Form 12. * significant interaction effects $p < 0.05$; ** $p < 0.001$.

Table 8.9 presents patient reported physical activity and leisure tasks in daily living at the beginning and end of follow-up. Data presented are number of patients (percentages).

Table 8.9 Self-reported physical activity level and leisure capability at baseline and at the end of follow-up between groups.

	Pre-surgery		14 weeks post-surgery	
	FET (n=25)	ESMET (n=26)	FET	ESMET
Physical activity				
Walking device	8 (16 %)	5 (10 %)	-	-
Indoors	14 (28 %)	14 (28 %)	1 (2 %)	0
<1km	2 (4 %)	5 (10 %)	15 (30 %)	1 (2 %)
>1km	1 (2 %)	2 (4 %)	8 (16 %)	9 (18 %)
Unlimited	-	-	1 (2 %)	16 (32 %)
Leisure				
No household	1 (2 %)	0	-	-
Minimal	17 (34 %)	12 (24 %)	-	-
Light yard	7 (14 %)	14 (28 %)	20 (40 %)	1 (2 %)
Heavy yard	-	-	3 (6 %)	2 (4 %)
Dance	-	-	2 (4 %)	19 (38 %)
Sports	-	-	0	4 (8 %)
Competitive	-	-	-	-

8.7.2 Associations between PROMs and objective indices of physical, balance and muscle strength performance.

As observed from Tables 8.5, to 8.9 patients of both groups have reported higher levels of physical and QoL performance (PROMs) compared to objective physical performance. Two-tailed probabilities were used due to the exploratory nature of this study. A few weak to moderate statistically significant levels correlations have been identified between PROMs [KOOS, KOS-ADL, SF-12] and objective measures of physical performance [TUG Test] (ranging from $r = -0.34$ to -0.41 ; $p < 0.05$). Weak to good statistically significant correlations were recognised between pain [VAS] and objective physical performance [TUG] (ranging from $r = 0.35$ to 0.66 ; $p < 0.05$) in the post-surgery assessment sessions. Low to moderate inverse (-0.30 to -0.61 ; $p < 0.05$) correlations have been identified between PROMs [VAS, KOOS, KOS-ADL, SF-12] and objective measures of balance in the post-surgery follow-up assessment sessions, especially for the operated limb. Low inverse levels correlations (ranging from $r = -0.31$ to -0.37 ; $p < 0.05$) have been identified between pain [VAS] and objective measures of muscle strength as well as PROMs [KOOS, KOS-ADL] and muscle strength (ranging from $r = 0.30$ to 0.41 ; $p < 0.05$) at the 14th week assessment session.

8.7.3 Associations between PROMs and objective indices of functional, balance-related and muscle strength for the experimental [ESMET] group.

Modest correlations were confirmed between measures of physical [TUG] and neuromuscular [PF] performance ($r = -0.53$; $p < 0.01$) at pre-surgery. A significant modest inverse correlation was also identified between sensori-motor index JPE_{25°} and physical performance index [TUG] ($r = -0.45$; $p < 0.05$) at pre-surgery.

When exploring the correlations amongst change scores (baseline to 14 weeks) only modest correlations were identified (Table 8.10). Patterning of change scores between functional and sensor-motor indices mimic the changes in effect sizes for outcomes of neuromuscular performance, muscle size and knee ROM, but similarly suffer from weak correlations, which fail to endorse a clearly defined mechanistic pathway.

Table 8.10 Pearson's Correlation Coefficients for change scores (between baseline and 14 weeks) of measures of functional mobility, sensori-motor function and direct and indirect measures of neuromuscular capacity, muscle size and knee ROM.

	PF	EMG-derived measures	Muscle size (CSA _{RF})	ROMext	Pain (VAS)	Sensori-motor function
Functional Mobility (TUG)	-	-	-	-0.4*	-	0.4*
Sensori-motor function (JPE %)	-0.4*	-0.4*	-	-	-	1.0*
Balance	-	-0.4*	-	-	0.4	-
PF	1.0	-	-	-	-	-

PF: Peak force; TUG: Timed Up and Go; EMG: electromyography; VAS: visual analogue scale; JPE: Joint position error; CSA_{RF}: Rectus femoris cross sectional area. * $p < 0.05$.

8.8 Discussion

This discussion will review and evaluate the context of the findings of this RCT study. The potential mechanism(s) that might have driven any observed changes in the study's primary outcome, as indicated potentially by patients' patterns of concomitant changes in performance on the selected secondary outcome measures, and by potential relationships amongst outcomes will receive further scrutiny. Moreover, considering the findings from the single-measurement reliability study (Chapter 7) and the literature, findings from the current main RCT study will be synthesised and evaluated in greater depth, in order to answer the main thesis' question.

The central aims of the RCT study were formed because of the “gaps” in the evidence (identified by the background literature and survey) for efficacy of SMT rehabilitation in contemporary practice. The current supporting evidence for clinimetric properties of outcome measures used within TKR rehabilitation (Chapter 3) and the reproducibility and single-measurement reliability study also contributed to the selection of optimal outcome measures and the interpretation needed to reflect the mechanism-driven changes for clinicians working in TKR rehabilitation.

For simplicity, the discussion will be divided into three main sub-sections: A) Did the enhanced sensori-motor exercise training programme offer group-based evidence on the indices of function, indices of balance and indices of sensori-motor performance in a TKR clinical population compared to a usual care programme; B) Did the enhanced sensori-motor exercise training programme have any effect on the indices of neuromuscular, musculoskeletal and psycho-physiological performance in a TKR clinical population compared to a usual care programme (This sub-section also considered the MDC and MCID properties of selected indices, in order to offer corroborating evidence on how individual patients might have been positively affected by the ‘intervention’); C) Interpretation and potential mechanisms of action associated with the study’ findings; and D) Limitations and clinical implications.

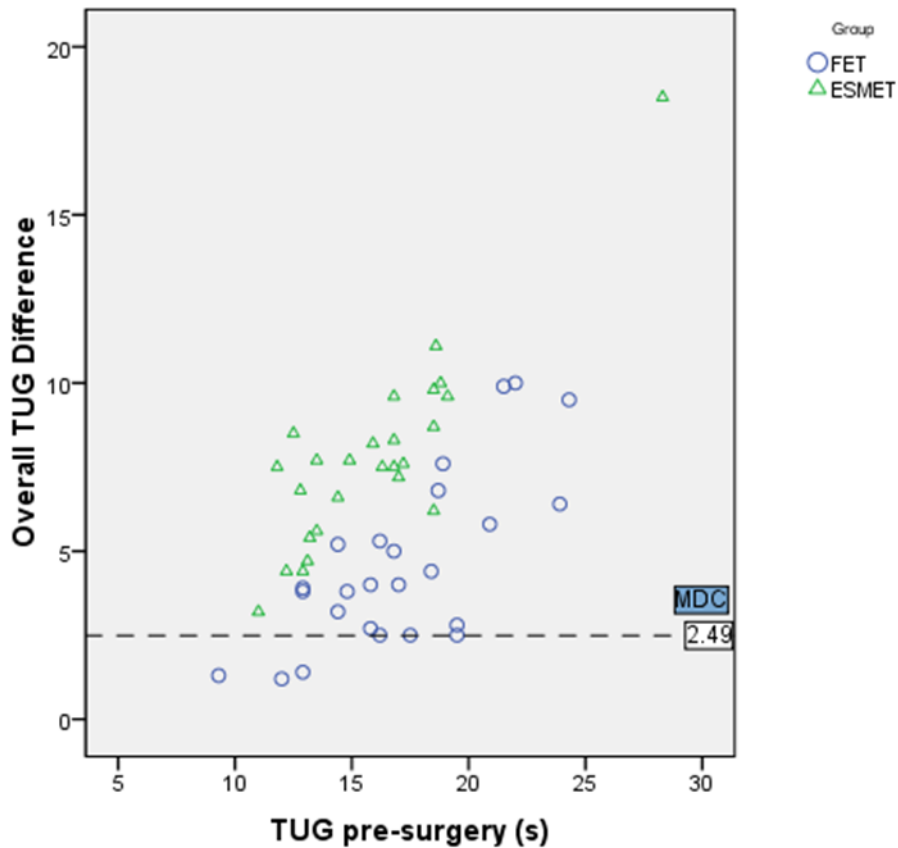
A) Did the enhanced sensori-motor exercise training programme have any effect on indices of functional performance, balance-related and sensori-motor performance in a TKR clinical population compared to a usual care programme?

The principal finding of this RCT study, which also has considerable clinical importance, was that patients undergoing TKR who performed the enhanced sensori-motor exercise training programme demonstrated superior gains in functional indices compared to those performing the functional exercise training programme. As well as having demonstrated greater efficacy, the enhanced sensori-motor exercise training had been well-tolerated by patients, even when it had been initiated soon after surgery (2 - 3 weeks post-surgery) and importantly, these advantages were delivered successfully within an environment of self-managed care. Thus, in an albeit modestly-sized sample of patients undergoing TKR, the same prescribed duration of rehabilitative training has yielded significant improvements in almost all outcomes. While minimally-important clinical differences (Sloman *et al*, 2016) for outcomes remain typically elusive in this clinical population (Keurentjes *et al*, 2016), the extent of the gains favouring enhanced sensori-motor enhanced exercise training suggest that they are likely to be relevant clinically, and that the findings warrant further verification in subsequent well-controlled clinical trials.

Primary clinical outcome (TUG)

Restoration of function is always the main aim in rehabilitation and as such, assessment of function via the TUG Test was chosen as the primary outcome for this study. The ESMET programme delivered with an exercise guidebook (for twelve weeks), resulted in a reduction of 3.2s greater, compared to usual care, in the time taken to complete the loco-motor functional outcome of TUG. Patients' individual improvement scores for the Timed Up and Go Test from baseline to the end of training are shown in Figure 8.13 and offered an example of further corroborating evidence for the superiority of enhanced sensori-motor exercise training for which in contrast to controls, all participants exceeded the MDC (2.49s) (Kennedy *et al*, 2005). Therefore, alternative (H1) hypothesis of the study has been accepted, as there was a difference in the effects of early initiation of self-managed, enhanced sensori-motor exercise training with those of functional exercise training (usual care) on indices of functional performance (TUG Test) in patients following TKR.

Figure 8.13 Individual patient's position in terms of MDC in the enhanced sensori-motor exercise training and functional exercise training on functional indices assessed by the TUG Test.



MDC: Minimal detectable change; TUG: Timed Up and Go Test; TKR: Total knee replacement; ESMET: Enhanced sensori-motor exercise training group; FET: Functional exercise training group.

At the end of the follow-up (14th week), and by comparison to pre-surgery (baseline) scores, this improvement resulted in a reduction of 7.8s (95% CI 7.1 to 8.4s) and a reduction of 4.6s (95% CI 4.0 to 5.2s) for the ESMET and FET group, respectively. This magnitude of treatment effect ($d = 2.8$) is above what is considered a minimum detectable change (MDC = 2.49s, $d = 0.43$) (Kennedy *et al*, 2005; Mizner *et al*, 2010). In the literature, a SEM of $\sim \pm 1.1$ s has been reported as an estimate of the measurement reproducibility of this outcome. The MDC values for all the outcome measures in the main study of the thesis (Chapter 8) were derived from the SEM for the study population, and showed a SEM for the TUG Test of $\sim \pm 0.6$ s (68 % confidence limits) and an MDC of ± 1.7 s (95 % confidence limits). Under circumstances in which patient' assessments are reliant on a single measurement of an outcome, changes greater than the MDC must be detected for the clinician to be

sure within the specified confidence limits, that his/her patient has made a true change i.e. beyond random error (de Vet *et al*, 2011). On the basis of the excellent consistency and agreement results for the TUG, a finding of almost 2s, can also be recommended to clinicians as the minimum value required to demonstrate a real change in the functional capability of an individual patient undergoing TKR.

The greater gains in objective measures of functional performance (Timed Up and Go Test) recorded in the current study (~50 %) compared to those gains noted for studies with similar conceptual designs in the systematic review (~25 %) (Moutzouri *et al*, 2016a), might be attributable to the latter's delayed initiation of sensori-motor exercise training (two months post-surgery compared to the current study's 2 - 3 weeks), with an earlier initiation consequently potentiating the degree of functional recovery (Mizner *et al*, 2005a). It was interesting to note that the study's findings suggest that there would be no particular advantages associated with efficacy or logistics in a cessation of conditioning before the scheduled end of rehabilitation for either the ESMET or FET programmes. This interpretation centres on the fact that gains in functional performance capabilities, as measured by the TUG Test, of patients in both the FET and ESMET groups, had occurred progressively over the 14 weeks of rehabilitation' monitoring.

Comparison with previous relevant work is possible cautiously in the context of the study by Liao *et al* (2013), which shares the closest design to the present study, and this study had found a ~1.5s difference in the reduction of time taken to perform the TUG test for the experimental group (compared to the control group). Importantly however, the latter study had not used a time-matched comparison, and instead, had compared the effects of an additional volume of balance-related exercises within a rehabilitation programme, to the effects of the functional programme used in contemporary practice for the TKR patients (eight week intervention period; started > two months post-surgery).

Secondary clinical outcomes

Balance-related and sensori-motor performance indices

The alternative hypothesis (H2) was accepted, as for balance-related and sensori-motor performance the ESMET group showed statistically significant greater improvements. Enhancing the functional exercise programme (usual care) with

sensori-motor components led to greater improvement in balance control. Statistically significant improvements in balance control were shown over time for the ESMET group compared to the FET group, with similar responses noted for both legs. Overall the ESMET group exhibited an improvement in the OSI of 1.5 degrees (~40 % greater improvement compared to the FET group) overtime. In the current study, the magnitude of the treatment effect was relatively large for the ESMET group ($d = 1.3$ versus $d = 0.3$ for FET). The studies that were most comparable to the current study in terms of balance assessment post-TKR (Gstoettner *et al*, 2011; Swanik *et al*, 2004), found lower percentage improvement scores (~15 %), between the enhanced and control groups. However, the study by Gstoettner *et al* (2011) evaluated the effect of a six week pre-operative proprioceptive programme and the study by Swanik *et al* (2004), evaluated the effect of a usual care programme (with no sensori-motor focus). Overall, methodological differences make meaningful comparisons difficult. The OSI has been found as the most reliable of the three indices (overall, antero-posterior and medio-lateral) produced by the Biodex Balance System (Cachupe *et al*, 2011, Perreira *et al*, 2008) (please see Section 3.4, pages 81-82). The OSI has been reported to have good clinimetric properties with a SEM indicating a reproducibility error of 1.06 degrees of tilt (Cug & Wilkstrom, 2014). The ESMET group has shown a performance improvement greater than the SEM reported in the literature, suggesting that a good proportion of the total number of patients might have performance gains exceeding error limits associated with a single measurement. As a consequence, these patients might have benefitted from the ESMET formulation of sensori-motor-focused training.

Superior gains in proprioceptive performance capabilities for the ESMET group compared to control (~25 %), which had been most pronounced at 25 ° of knee flexion for the operated leg, were found at the end of the rehabilitative period. However, results for the 60 ° target angle showed that the improvement was of the same magnitude amongst limbs. Force error, again showed a marked reduction ~30 %, i.e. better performance with the ESMET throughout the follow-up period and which had been more pronounced for the operated limb. The only study so far investigating JPE after SMT had been unable to detect significant gains in proprioception, but had presented evidence from patients undergoing both knee and hip replacement surgeries, with a much shorter duration of training (3 weeks) and some sensori-motor exercises in non-weight bearing positions via a sling system

(Pohl *et al*, 2015). In terms of errors associated with the reproducibility of measurement, the literature has reported a $SEM_{68\%CI}$ of $\pm 2.3^\circ$. In the current study, joint position error measurements had achieved moderate to high reliability ($ICC_{(2,1)}$: 0.60 - 0.83) and clinically acceptable $SEM_{68\%CI}$ (3.0° for JPE_{60° and 7.0° for JPE_{25°) during all three testing occasions for both operated and non-operated limbs and for both target angles (25° and 60°). However, the $MDC_{95\%CI}$ was found as 20.4° , showing that a noticeable change in sensori-motor performance for an individual patient would need to occur in order for the change to be confidently interpreted as being real. Gains in proprioception capability in the current study reached a mean 13.0° change over time for the ESMET group (6.8° difference in change over time compared to control). As already mentioned, a MDC value had not been presented for the JPE prior to this thesis. However, JPE appears to offer good consistency but relatively large error variability. Therefore, a large change of $\sim 20^\circ$ on the performance of JPE or more would be required to demonstrate a 'real', and systematic change (i.e. not due to inherent random biological or technical variability of the measurement) in the sensori-motor performance of a TKR patient. The clinical relevance of this finding, both for an individual patient, and for the group of patients as a whole, is that the 12-week of SMT intervention had not been potent enough to confer with confidence the relatively large measured changes in performance (large ESs over 20°) needed for a clinician to detect real gains made by the patient(s).

B) Did the enhanced sensori-motor exercise training programme have any effect on indices of neuromuscular, musculoskeletal and psychophysiological performance in a TKR clinical population compared to a usual care programme?

The rationale for investigating the effects of enhanced sensori-motor exercise training on measures of neuromuscular and musculoskeletal performance, in addition to the functionally-relevant outcomes, was primarily because balance defects, documented in TKR patients, were correlated to many factors that are considered as contributors to balance control, such as pain, loss of proprioception, as well as decreased muscle strength (Ahmed, 2011). A convincing body of evidence suggests that improving muscle strength is one of the key components of the recommendations for TKR rehabilitation, as it has been shown to play a vital role in functional recovery for these patients (Bade *et al*, 2010; Meier *et al*, 2008; Mizner

et al, 2005; Pozzi *et al*, 2013; Thomas *et al*, 2014). Failure to address quadriceps' weakness leads to chronic impairments that limit the long-term functional gains possible following TKR (Meier *et al*, 2008). Loss of muscle strength post-operatively has been shown to be a major drawback for these patients' function and falls' risk. Accumulating evidence has supported the importance of the central nervous system in regulating movement in order to reach proper muscular firing patterns for maintaining joint stability. This contrasts with an emphasis on strengthening muscles in isolation, which are local to a joint. As a result, patients would be able to develop the motor skills to deal with the destabilising forces encountered during ADL.

Moreover, secondary neuromuscular indices were used as explanatory variables of the potential mechanism driving responses to SMT. Therefore, it could be indirectly argued that any potential effects of ESMET could be attributed to neurophysiological, morphological or a combination of the two responses if findings provided relevant evidence.

The experimental hypothesis (H3) could only be supported partially because greater gains in the ESMET group (compared to usual care) were only presented for neuromuscular and muscle size performance and not for knee ROM.

Neuromuscular performance indices

In the current study, enhancing the usual care functional exercise programme with sensori-motor components led to twice the increase in strength for the quadriceps muscle (PF) at the end of the follow-up assessment for the ESMET group (52 %, 95% CI 24.0 - 25.8) compared to the FET group (28 %, 95% CI 10.7-14.1). No other relevant study had previously evaluated quadriceps muscle' strength with the supplementation of SMT. The only study that showed increase in quadriceps strength earlier than two months was the study by Bade *et al* (2010) that had implemented a high intensity rehabilitation programme with weekly milestones on resistance progression and strengthening exercises performed not only with weights, but also with body-weight exercises as well (e.g. step-ups, side step ups, single limb stance), mimicking ADL. In the literature, the SEM for quadriceps PF has been reported as ~11 N and the MDC at the 90 % CI, as ~25 N. In the current study, SEM was found to be ~3 N and the MDC at the 95 % CI as 8.6 N. Findings of the current study showed group mean gains of 25.1 N (12.7 N greater compared to

control) over time. Therefore, in terms of potential for the clinical relevance of measurements of strength, changes greater than ~9 N must be detected by the clinician to assure meaningful differences associated with single measurements at the individual level.

No studies implementing SMT in TKR patients had previously investigated changes in muscle strength, but have rather focused on performance-based and self-perceived functional outcome measures. Ahmed (2011), implementing a similar conceptual design to that of the current one in patients with knee OA, also found that SMT can elicit improved neuromuscular performance. In studies investigating quadriceps muscle strength post-surgery, using usual care programmes, reductions (~17 %) were noted for the operated limb (Mizner *et al*, 2005; Stevens-Lapsley *et al*, 2010). Therefore, usual care programmes were not capable of reversing the quadriceps muscle' strength loss that has been identified as being present for up to six months post-surgery (Stevens-Lapsley *et al*, 2010; Valtonen *et al*, 2009). However, when, an early (within two weeks post-surgery) high intensity training programme had been implemented, quadriceps muscle' strength showed an improvement of 7 % at twelve weeks post-TKR, and a marked improvement of ~30 % was achieved at twenty-six weeks post-TKR in the operated limb (Bade *et al*, 2010). In another study, implementing an enhanced twelve week resistance exercise programme with eccentric training, a 15 % increase in quadriceps muscle' strength had been observed (LaStayo *et al*, 2009). Therefore, it would seem that with usual care programmes, recovery of quadriceps' strength requires approximately six months. However, when early post-surgery enhanced training strategies are implemented, quadriceps' strength seems to improve to the same extent, within the first twelve weeks, post-TKR. Although the effectiveness of exercise as a rehabilitation modality in TKR is accepted, the exact dosage/intensity of exercise that can reverse the decline of quadriceps strength within the first two months after surgery has yet to be established.

Greater gains (~45 %) in neuromuscular performance, particularly for EMG-derived measures (peak amplitude and RMS), were elicited for the ESMET group compared to control, and these improvements had been most pronounced for the operated limb. Therefore, the increase in PF as supported indirectly by the increase in EMG activity, can be interpreted as being driven by an increase in the neural drive (central

factors), which might be defined potentially defined by an increase in the number of active motor units and their firing rates. Since EMG-derived indices showed good consistency and agreement levels, there would be a likelihood that a $MDC_{95\%CI}$ (MDC representing $\pm 95\%$ confidence limits associated with a single measurement) of 0.3 mV could be applied usefully to clinical scenarios involving individual patients, in order to enhance the clinical interpretation of alterations in neuromuscular performance capability. No published study so far has investigated muscle activation parameters during static peak force as measured with EMG in TKR patients. However, a number of studies have been published that have assessed dynamic muscle activation parameters during gait or specific functional tasks such as a step-up task or overcoming an obstacle (Benedetti *et al*, 2003; Byrne & Prentice, 2003; Byrne *et al*, 2002; Mandeville *et al*, 2008; Thomas *et al*, 2014; van der Linden *et al*, 2007). However, the strength of relationship between force and dynamic muscle contraction is reduced compared to isometric contractions (Christensen *et al*, 1995). Therefore, the latter results cannot be directly comparable with those of the current study.

Musculoskeletal performance

Patients with knee OA present with reduced knee flexion when performing locomotor functions and therefore, develop compensatory mechanisms to achieve ADL activities (Walker *et al*, 2001). Following TKR, although joint stiffness is restored, muscle shortening and existing compensatory mechanisms have to be reversed in order to achieve improved functional ability. In the current study, there was no statistically significant difference over time between groups for knee extension ROM (increase of about 4° for both ESMET and FET group at the end of follow-up at 14 weeks). On the other hand, statistically significant results were found for knee flexion ROM, with the ESMET group demonstrating an increase of $\sim 2.5^\circ$ whereas the FET group demonstrated a loss of more than 2° in the 14th week during follow-up. Both ESMET and FET groups showed similar patterns of improvement on ROM during knee extension manoeuvres, suggesting that enhanced SMT conditioning did not confer any particular advantages for this aspect of musculoskeletal performance. Regarding the results for knee flexion ROM, between-group differences were revealed over time ($\sim 2\%$ greater gain favouring the ESMET group), suggesting that the enhancement to sensori-motor components of training within ESMET had facilitated greater gains in functional ROM during knee flexion following TKR. In the

study by Fung *et al* (2012) that compared an enhanced balance programme (Wii-fit) with a standardised functional programme, matching the conceptual framework of the current study, they found an increase of ~17 % in knee extension and 1 % of knee flexion in both groups, within 6 - 8 weeks post-TKR. However, the aforementioned trial was underpowered to potentially detect only a relatively large difference in knee ROM, compared to what had been envisioned within the current study. Literature has shown a SEM of 2 ° to 3 ° and an MDC of 4 ° - 7 ° for knee ROM (Reese & Bandy, 2017). Therefore, while changes in the group mean responses for the ESMET and FET groups offer new insights into the patterning of musculoskeletal performance restoration following TKR, because the latter changes of the current study are within limits of single-measurement error, musculoskeletal measurement might not always offer usual discrimination of performance changes for individual patients.

Rectus femoris' CSA with the use of real time ultrasound was considered an interesting and novel measure to use, in order to evaluate how the muscle size 'behaves' during post-surgery recovery while it's being influenced by SMT, and whether potential changes in muscle morphology correlate, in TKR patients, with patterns of change in muscle strength' parameters. Moreover, the aim was to determine whether an enhanced sensori-motor exercise training programme can induce clinically meaningful changes in RF CSA, along with patient mobility. No study (neither implementing sensori-motor nor usual care programmes) on TKR patients has so far used real-time ultrasound to investigate muscle architectural parameters. A few studies have used CT scanning or MRI techniques to measure muscle size and composition of quadriceps along with muscle strength parameters (Rodgers *et al*, 1998; LaStayo *et al*, 2009; Valtonen *et al*, 2009). Previous studies suggested that there is a decline up to 20 % in the quadriceps' CSA of the operated limb in the early recovery phase (one to three months post-TKR) (Meier *et al*, 2008; Rodgers *et al*, 1998). The ESMET group in the current study demonstrated significantly increased CSA during relaxation, but more importantly, an increase during the contraction phase, at the 14 weeks post-TKR, and which was more pronounced for the operated limb (95 % CI 252.0 mm², ~73 %) compared to FET (95 % CI 156.7 mm², ~44 %). In the current study, SEM was recorded as 12.2 mm² for the rectus femoris CSA_{CONTR}, with a MDC of 35.6 mm². Changes in rectus femoris CSA showed gains of 252.0 mm² (95.0 mm² greater compared to control).

Therefore, a change of more than $\sim\pm 36.0 \text{ mm}^2$ in rectus femoris CSA could be recommended to clinicians to identify with confidence (95 % confidence limits). Nevertheless, because the current study's findings are novel, further research will be needed to fully contextualise the limits to measurement precision for architectural changes in muscle and potency (effect size) of any rehabilitative training programme. Real time ultrasound, used as a novel measure in the current study, might be considered to be clinically useful in TKR clinical populations to reflect training' induced morphological adaptations. 'real' performance changes after conditioning interventions for an individual patient.

Self-reported function, pain and psycho-physiological performance indices

The (H4) alternative hypothesis has been retained as the ESMET group presented with greater gains in self-perceived performance of function, pain and QoL. More specifically, the current study elicited a statistically significant (89 %; 6.0 cm, NPRS), and clinically-relevant (MCID = 28.6 %) (Sloman *et al*, 2016) reduction in the patients' perceptions of pain during the course of undertaking ESMET, which further endorses this type of approach over post-surgical usual care (FET) ($\sim 4.5 \text{ cm}$). In clinical trials of OA, analyses of the relationships between changes in NPRS scores and patient reports of overall improvement, demonstrated that a reduction of 2 cm on the NPRS would represent a clinically important change perceived pain (Farrar *et al*, 2001). Sloman *et al* (2006) reported that a more accurate predictor of perceived pain was achieved by converting the change in scores on the NPRS to percentages. Using this approach, an MCID of 28.6 % reduction in pain post-orthopedic surgery, had been identified. Early initiation and the mode of training may underpin these favourable improvements but these gains contrast dramatically with no statistically significant changes in pain being reported for studies with a similar conceptual design to that of the current one (33 % - 42 %; $\sim 1 \text{ cm}$) but involving delayed initiation of training (Liao *et al*, 2013; Piva *et al*, 2010).

The self-perceived outcome measures of function used in this thesis were the KOOS and the KOS-ADL. There appears to be no universally-accepted 'gold' standard assessment tools in this respect and so an array of outcomes was selected for use within the main study on the criteria of popularity of use and clinimetric quality. KOOS separates the scores of each sub-section, thus allowing better interpretation and correlation between the items of each subscale (Roos &

Lohmander, 2003). The functional performance of patients, as depicted by the KOOS subscale (Roos & Lohmander, 2003), suggests that an 8 - 10 point change in a KOOS score might represent a minimal perceptible clinical improvement (equivalent to MDC with 95 % confidence limits) following TKR. The KOOS, and also the KOS-ADL, have been differentially influenced over time between the enhanced sensori-motor exercise training and the functional exercise training group, with the ESMET group being significantly superior. Interestingly, the greatest improvement of the KOOS five subscales post-operatively, followed a similar ranking order for both groups (ESMET and FET), with the subscale of sports and recreation activities scoring highest followed by quality of life, then pain, then ADL, and lastly symptoms, over the 14 weeks of the assessment period. The difference in KOOS subscales over time ranged from ~25 - 34 units, which is well above the ten units that are considered as the minimum detectable perceptible change for KOOS following TKR (Roos & Lohmander, 2003; Roos & Toksvig-Larsen, 2003). Studies with a close similarity of design to the current study have used outcome measures such as WOMAC and LEFS to illustrate similar self-perceived characteristics as those within the KOOS. However, these outcome measures were not selected for use in the current study because they have neither been validated in the Greek language, nor depict the same range of patients' perceptions of symptoms, QoL, ability to perform ADL. Furthermore, each of latter outcomes perhaps emphasise the investigation of more demanding sports and recreational activities compared to those within the KOOS' dimensions. The studies by Monticone *et al* (2013), Nilsson *et al* (2009), and Ornetti *et al* (2008) have used KOOS to measure functional ability after TKR, with results that showed good responsiveness. The latter authors' findings have shown improvements of 11 - 15 units in three of the five KOOS subscales (pain, QoL and ADL) without however, mentioning details of TKR rehabilitation. Relevant findings are reported even from the first post-operative month (Stevens-Lapsley *et al*, 2011),

Moreover, in the current study, the ESMET group has shown a ~125 % (versus a ~78 % for control) change scores from baseline over time, respectively, in the KOS-ADL. These percentage change scores are higher than those reported in the literature, at three months (47 %), and at six months (57 %) post-surgery, involving a usual care programme (Mizner *et al*, 2005). The latter findings indicated that KOS-ADL has the capability clinimetrically to detect improvements and differences in

knee-related functional performance amongst patients undertaking a usual care and an enhanced sensori-motor exercise programme. Therefore, the sensori-motor elements incorporated within the usual care programme of training could explain these discrepancies in percentage changes amongst the current study's and those within the literature. In terms of responsiveness to change, KOS-ADL showed an effect size of 5.5 (for the ESMET, compared to 3.2 in the control group). Although of lower magnitude, large effect sizes (~1.3) have been reported in the literature following six months of post-TKR rehabilitation (Impellizzeri, *et al*, 2010).

The Short Form-12 (a shorter version of the SF-36) measures health functioning on two scales, physical and mental. The SF-36 inventory is perhaps amongst the most widely used to illustrate an individual's self-perceived psycho-physiological performance and perception of quality of life. However, SF-12 is more practical to use because of its brevity in measuring psychometric performance (Brazier & Roberts, 2004) and the lack of associated permission costs. It has been found to be associated with patient satisfaction after TKR (Scott *et al*, 2010). The percentage change scores for improvements within the SF-12 [physical] and SF-12 [mental] showed a significant superiority for the ESMET group (51 % and 37 %, respectively) compared to the FET group (29 % and 17 %, respectively) from pre-surgery over time. Although these percentage change scores are not exactly comparable with previous studies that have used the SF-36, findings in the current study have in general, shown greater magnitudes of change compared to those findings in the literature. The latter involved a ~30 % increase in overall SF-36 physical component scores elicited with SMT elements within a water-based environment (Liebs *et al*, 2013), and a ~43 % improvement with usual care programmes (Mizner *et al*, 2005), at three months post-TKR.

Nevertheless, the combination of superior gains in indices of functional, balance and sensori-motor performance derived from this specific mode of enhanced sensori-motor exercise training was accompanied by a clinically meaningful and superior reduction in the number of falls experienced by patients, with corresponding Timed Up and Go Test scores ($8.1 \pm 1.7s$) residing firmly within the time-frame for a minimally-important clinical criterion (13.5s) that is associated with critical progressions in falls' risk (NICE, 2013; Rose *et al*, 2002). Between group differences for the number of falls reported was associated with a *p*-value near 0.05 (*p* = 0.07),

(with the FET group reporting 2.4 falls and the ESMET group 1.9 falls for one year prior to surgery). It has been lately discussed that *researchers should recognise that a p-value without context or other evidence provides limited information* (Wasserstein & Lazzar, 2016). For example, a *p*-value near 0.05 taken, as in the aforementioned case, by itself offers only weak evidence against the null hypothesis. Therefore, it cannot be definitively reported that there was no difference between the ESMET and FET groups with regards to number of falls experienced pre-surgery. This may have implications concerning the fear or falling and the potentially resulting restriction of activities (Talley *et al*, 2014) that the ESMET group may experience at baseline compared to the FET group. One year prior to surgery all patients had reported at least one fall. However, it was observed that post-surgery, only three patients (~6 %) within the ESMET group (compared to twenty-two patients (~43 %) within the FET group who reported at least one fall) reported having experienced a fall. There had been a significant association between rehabilitation using ESMET and a reduction in the incidence frequency of falls ($X^2_{(2)}$; $p < 0.001$). However, the duration of follow-up was not equivalent to one year, as was the time that patients were asked to report falls prior to surgery, and that creates a bias as patients may experience falls after the endpoint of this study up to one year post-surgery. Moreover, the number of falls reported in the year prior to surgery was based on patients' recollection capability. Therefore, the elderly have difficulties in accurately recalling the occurrence of falls in previous periods, especially non-injurious falls (Ganz *et al*, 2005). Thus, a large part of the available data is susceptible to reporting, recording errors or recalling bias (Althubaiti, 2016). Self-reporting of falls over a 12-month period has been shown to be underestimated by ~ 33 % of actual falls (Garcia *et al*, 2015). No study implementing SMT during rehabilitation following TKR, has previously investigated the incidence of relative likelihood of falls. Observation studies have shown a reduction of falls after TKR, without however, reporting the complete absence of falls post-TKR (Swinkels & Allain, 2013), and a result that is notable for having almost been observed in the current study. Nevertheless, the latter observation requires corroboration in the future against the findings from more comprehensive studies focusing specifically on the effects of SMT interventions on the incidence of falls following TKR surgery.

Table 8.11 Key findings of main study of the thesis.

	Did the ESMET programme have an effect (compared to control) on the primary outcome measure of functional performance (TUG) within a TKR clinical population?	Did the ESMET programme have an effect (compared to control) on sensori-motor function, within a TKR clinical population?	Did the ESMET programme have an effect (compared to control) on neuromuscular, musculoskeletal and psycho-physiological performance within a TKR clinical population?	Did the ESMET programme have an effect (compared to control) on self-reported measures of function, pain and QoL within a TKR clinical population?
Factorial ANOVA	TUG was responsive to changes induced by the ESMET programme, as evidenced by ANOVA and effect size results (2.8). (Alternative hypothesis (H1) confirmed).	OSI and JPE _{25°} /JPE _{60°} were responsive to changes induced by the ESMET programme, as evidenced by ANOVA and effect size results (0.7 -1.4). (Alternative hypothesis (H2) confirmed).	PF and CSA, but not knee ROM, were responsive to changes induced by the ESMET programme, as evidenced from the ANOVA and effect size results (1.8 - 3.7). (Alternative hypothesis (H3) partially confirmed).	KOOS, KOS-ADL, SF-12 and NPRS were responsive to changes induced by the ESMET programme, as evidenced by ANOVA and effect size results (2.1 to 6.5). (Alternative hypothesis (H4) confirmed).

<p>TUG demonstrated excellent reliability (ICC > 0.9) and agreement with MDC₉₅ of 1.7s, and can therefore be recommended for use clinically within a group-based design and potentially, with individual patients.</p>	<p>JPE demonstrated good reliability (ICC > 0.7), but high error variability, with MDC₉₅ of 20.4°, and can therefore be recommended for use clinically, but only within a group-based design.</p>	<p>PF and CSA demonstrated excellent reliability (ICC > 0.9) and agreement with MDC₉₅ of 9 N and 36.0 mm², respectively and can therefore be recommended clinically within a group-based design and potentially, with individual patients.</p>
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TUG: Timed up and Go Test, OSI: Overall stability index; JPE: joint position error; ESMET: enhanced sensori-motor training; PF: peak force; CSA: cross-sectional area; TKR: total knee replacement; MDC: minimum detectable change; ICC: Intraclass Correlation Coefficient.

Compliance with home-based exercise programmes: Self-reported volume of exercise and therapist interaction effect

An important issue is often that home-based physiotherapy exercise has a low ‘uptake’ in participation, leading to patients being not compliant with exercise prescriptions for training and ultimately, leading to them having poorer functional mobility. It is known that exercise adherence can affect treatment outcomes, with factors such as pain, physical function, physical performance and self-perceived effect of exercise being higher in those with better adherence especially in the elderly (Pisters *et al*, 2010). Therefore, low levels of adherence may limit the effectiveness of prescribed exercise. McLean *et al* (2010) found that effective adherence to exercise at home only occurs for a short period. Studies investigating the effects of additional balance exercise programmes within usual care programmes, were mostly outpatient-based (Fung *et al*, 2010; Liao *et al*, 2013; Piva *et al*, 2010). However, none had reported the adherence’ level to the exercise prescription. In the current study, a home-based programme was selected in order to make the programme feasible within the Greek system of health-care practice (as indicated by the clinical survey performed, Chapter 4) and to empower patients in their rehabilitation progress. In order to increase the patients’ compliance (ESMET and FET) with the prescribed exercise programmes a number of strategies were used as suggested and confirmed by the literature (Resnick *et al*, 2008; Pisters *et*

al,2010; Peek *et al*, 2016): a) written instructions via an informative guidebook with illustrations of the prescribed exercise programmes were provided for each group, b) activity monitoring via exercise diaries, and c) patients in both groups were encouraged to telephone or visit the physiotherapist *ad libitum* in case they encountered some difficulty. This support strategy involved dealing with queries about exercises, exercise maintenance, problem solving, discussion and recommendations.

As part of the assessment of compliance, the duration (daily) and frequency (weekly) of home exercise therapy (for both ESMET and FET groups) were recorded by patients using a weekly diary of physical activity and a specific questionnaire form. This was obviously based on patient-reporting of physical activity and exercise levels, which have inherent challenges to objectively-determined performance. Delayed recording in the exercise log may lead to inaccurate recall of details such as the date, frequency, and duration of exercise or missed recording of the event altogether (Sallis & Saelens, 2000). In addition, some studies have suggested that participants tend to over-report their exercise levels in terms of frequency, duration, and intensity (Sallis & Saelens, 2000; Yuen *et al*, 2013). In the current study, the exercise compliance level was good for both groups (~83 % vs ~72 %), as the literature a mean adherence rate of 63 % has been reported among elderly populations with rates being higher in programmes that are less than six months in duration (Martin & Sinden, 2001; Rejeski, *et al*, 2005; Tsauo *et al*, 2005).

However, findings showed some group discrepancies amongst the time reportedly spent exercising and in the weekly frequency of exercise. Exercise compliance as analysed by patient-reported diaries showed a statistical significance amongst groups with the ESMET group presenting with a ~10 % higher compliance compared to the FET group. The nature of the 'time-matched by prescription' experimental design for rehabilitation conditions within this study had required careful consideration of what would constitute equivalent instructions to ESMET and FET groups. Both ESMET and FET groups had been encouraged, as per usual clinical practice, to seek advice equally should any of the rehabilitative exercises were not fully understood. However, the ESMET group, because they would be undertaking exercises that were entirely novel to this study and clinical practice at

this stage of patients' recovery post-TKR, were encouraged to present for physiotherapy oversight of training during one session per week (for only the first six weeks of the training programme; an attendance rate of ~78 % was recorded), to ensure safe and effective performance of the novel SMT exercises (as suggested by the Ethical Committee). Therefore, this finding of discrepancy in the exercise compliance may be attributed to the patient-therapist interaction phenomenon (known as the Hawthorne effect and social approbation). The literature has shown that patients value highly the communication attributes of physiotherapists relating to the interpersonal skills, manner and teaching ability (O'Keefe *et al*, 2016). Interestingly, communication ability and other personal attributes of physiotherapy staff are valued as more important than the content or outcome of treatment (Potter *et al*, 2003). Empathetic and caring physiotherapists may achieve higher levels of physical activity for their patients by motivation (Peiris *et al*, 2012). A positive interaction in musculoskeletal physiotherapy can positively influence treatment outcomes such as pain, disability, health status and satisfaction with care (Hall *et al*, 2012; O'Keefe *et al*, 2015). In the current study, it is plausible that the necessity for extra indirect interaction with a clinician might have provoked inadvertently some form of social or clinical approbation from patients, with concomitant willingness to register amplified ratings for physical activity in general.

However, the clinical relevance of this phenomenon has not been demonstrated definitively. A recent systematic review by Pesavento *et al* (2017) comparing models of supervised versus non-supervised rehabilitation in patients after TKR showed inconclusive results. An older systematic review by Coppola *et al* (2008) revealed evidence to suggest that independent home exercise is as beneficial following knee surgery as supervised physical therapy, most clearly for muscle atrophy and ROM; possibly for strength and function. A study with chronic lung disease patients compared an intervention including weekly phone calls and one home visit over a 3-month period with a control group. This study found a short-term difference in minutes of exercise undertaken, between the intervention and the control at 20 weeks ($p < 0.05$) (Steele *et al*, 2008). However, this difference was absent at one-year follow-up. More specifically, the study by Bailey *et al* (2015) examined the influence of the patient-therapist interaction by using a third group matching the programme of exercise rehabilitation used in the control group but with purposeful minimised attention and assessor-patient interaction during rehabilitation for ACL

injury. This third group were only assessed pre-operatively and at 48 weeks post-operatively, compared to the control group rehabilitation that were assessed on five separate occasions (pre-operatively, 6, 12, 24 and 48 weeks post-surgery). Improvement patterns were not significantly different in functional, neuromuscular or musculoskeletal outcomes between control groups indicating that clinical approbation by patients had not contributed to the outcome.

Nevertheless, ESMET and FET groups showed equivalent levels of decline in physical activity at the first post-operative assessment at 8 weeks compared to baseline, whereas at the final follow-up (14 weeks), ~ 57 % and ~ 44 % of patients in the ESMET and FET groups, respectively, had reported increased levels of physical activity (please see Table 8.9). It's indeterminate whether the latter relative increase in physical activity for the ESMET group was as a consequence of superior gains in outcomes for this group compared to those of FET, or might have inadvertently contributed to the conditioning effects, despite the study's novel time-matched design by prescription. It must also be remembered that any group differences in physical activity levels reflect self-reported levels, and not necessarily actual levels of activity. Any such interpretations would inevitably need to be made with extreme caution, given the self-reported nature of data acquired by an ad hoc design of diary and report form.

Additional informal physical activity has the potential to elicit responses over and above those anticipated as a systematic effect of the ESMET, but also, provoke an inferior responses should the interaction of additional activity and the prescribed conditioning be sub-optimal for any given patient. The author would argue that on balance, any subtle episodic variations in activity of this type would intrude minimally on the outcome of this study, and would be subsumed effectively within the wider and uncontrolled variations associated with discrepancies between the actual volume of conditioning undertaken (which had not been formally recorded during this home-based study) and those that had been prescribed for patients.

Outcome measures selected

The choice of outcome measures used within the thesis' main study was mostly driven by their relationships and specificity to the characteristics of the rehabilitative conditioning. As the aim of the intervention had been to enhance patients' functional

and sensori-motor performance, relevant indices were selected. The indices selected have been tested for validity and responsiveness, and most of them have been extensively used in the TKR literature. Clinimetric properties for selected indices were presented in Chapter 3. Moreover, the reproducibility and single-measurement reliability study performed in the current thesis, presented in Chapter 7, showed good to excellent characteristics of measurement error for the outcome measures that had been used. The choice of the selected indices was based on each outcome's a) clinimetric properties (Chapter 3), b) frequency of use in relevant literature and, c) practicability (time-related utility, likely patient' tolerance, and the availability of relevant equipment). Some indices used, were more specific and objective (or otherwise labeled as performance-based, such as TUG, balance, JPE, PF, ROM), others were characterised as being objective but novel in their use within this sub-group of patients (FE, CSA), and lastly, others were reliant on the self-perception of capability by the individual patient and reflect a more global and holistic perspective on physical function and quality of life (such as NPRS, KOOS, KOS-ADL, SF-12).

Performance-based measures have been shown to be more sensitive to capturing changes in physical capabilities compared to PROMs, as patients tend to over-estimate their ability after TKR when pain levels are reduced (Stratford *et al*, 2009). This observation justified using the TUG as a primary outcome measure because it quantifies performance as opposed to offer a qualitative perception of performance. Categories of outcomes were selected in an attempt to explain mechanistically, any potential effects on the primary outcome that might have been elicited by SMT. More specifically, it had been expected conceptually and from evidence within the literature, that any changes in objective functional improvements (physical [TUG] and balance performance), might have been attributed to neurophysiological (sensori-motor, neuromuscular) or morphological factors (muscle CSA).

Findings from objective measures compared to self-reported measures

Both patient-reported and performance-based measures of physical function and QoL have been used to evaluate functional outcomes after TKR. Patient-reported measures are the most commonly used as they are less expensive, less time consuming and reduce the number of patients lost at follow-up because they do not require a clinical visit. They provide useful information related to patients'

perceptions of physical function, but there is a burgeoning body of evidence that suggests patient-reports fail to capture the actual change in functional performance early after TKR, potentially due to the fact that pain is eliminated. Physiotherapy providers are being asked to use PROMs to evidence the quality of their care, alongside other metrics such as safety and patient experience data. Significantly the CSP included PROMs in their 2012 'Any Qualified Provider' (AQP) national specification for musculoskeletal physiotherapy (CSP, 2012). In some cases, the discrepancies in patients' reporting of limitations and their actual clinical changes are considerable. In the literature, three of five KOOS subscales significantly improved by one month after TKR and all five significantly improved by three to six months after TKR. In contrast, performance-based measures (6MW, TUG, SCT, and quadriceps strength) all significantly declined from pre-operative values by one month after TKR and significantly improved from pre-operative values to those recorded at three months and six months after TKR. Similarly, deterioration in scores for performance-based measures compared to pre-operative values were not always perceived as being clinically meaningful by patients (Mizner *et al*, 2011; Stevens-Lapsley *et al*, 2011). More specifically, while patients had perceived that their ability to negotiate stairs is better on the KOS-ADL at one month post-TKR compared to the pre-surgery, their times on the SCT had actually deteriorated by nearly 30 % during that interval. Patients also reported less limitation in their ability to walk and rise from a chair compared to their pre-operative assessment, yet their objectively-recorded times on the TUG had slowed by 12 %. The average time to complete the performance-based functional tests returned to pre-operative levels by two months after surgery (Mizner *et al*, 2011; Stevens-Lapsley *et al*, 2011). There had been an 18% improvement in the TUG and a 36 % improvement in the SCT, from the pre-operative test to three months post-surgery. During the exact same period of time, a 26 % improvement in SF-36 physical component score and a 78 % improvement in the KOS-ADL had been recorded concomitantly (Mizner *et al*, 2011).

In the current study, both objective measures and PROMs were able to differentiate amongst group' performance and showed marked improvement at 14 weeks post-surgery. However, again changes in PROMs from baseline to the end of the follow-up period showed greater magnitude of improvements (for example, KOS-ADL improved by 125 %) compared to objectively-measured functional performance

capacity (for example, the TUG Test improved by 49 %). Therefore, PROMs in the current study also showed discrepancies compared to objective scores, again potentially due to significant pain reduction post-TKR. Inverse relationships were found between the objective TUG, muscle strength PF and overall balance indices (OSI) and the PROMs that were limited in clinical relevance ($R^2 < 0.26$) in patients undergoing TKR. Interestingly, no associations were found between TUG and pain' measures. Therefore, TUG and PROMs were essentially contributing independently to the description of patients' functionality. This might be explained by the fact that TUG was not correlated with pain, whereas the literature highlights a strong relationship between patient-reported scores and pain perception.

This finding is similar to the evidence from relevant studies that also reported weak correlations between PROMs and functional performance (TUG) before TKR ($r = -0.19$ to -0.29) and moderate correlations up to three months after surgery (Gandhi *et al*, 2009; Maly *et al*, 2006; Stratford & Kennedy, 2006). Stevens-Lapsely *et al* (2011) and Mizner *et al* (2011) observed that while patients reported less limitation in their ability to walk and rise from a chair compared to their pre-operative condition in KOS-ADL, their time in performing the TUG had however, slowed by 12 % at one month. Piva *et al* (2010) found that PROMs of function (such as WOMAC and LEFS) do not capture the same information as the performance-based tests, and that performance-based tests are more sensitive to change and less influenced by pain. In the literature, slightly higher correlations ($r = 0.26$ to 0.34) were found between the objective measure, TUG, and measures of self-perceived psycho-physiological performance (SF-36, SF-12) ($r = 0.25$ to 0.74) (Gandhi *et al*, 2009, Hohmann *et al*, 2013).

The combination of findings from the literature and from those within the current study suggested that PROMs and TUG appear to have very few correlations. These few, weak correlations might give credence to a mis-matching of patients' perception of physical status capabilities and the true extent of their objective functional performance capacities. Importantly, in clinical practice if the patient's perception is that he/ she is better than his/ her actual functional capabilities, then this potentially could increase the risk of the patient choosing to undertake activities for which he/ she was not properly prepared. Conversely, if the patient doesn't feel capable, possibly due to anxiety or depression, then it might result in the patient's sub-optimal

efforts in rehabilitation. Therefore, the need for inclusion of both performance and PROMs of functional performance is highlighted if time and financial resources are available. If the resources are available then in terms of performance-based measures, muscle strength and balance performance should be clinicians' primary choice. If however, the resources are not available then performance-based TUG is a reasonable option that reflects patient's true functional mobility skills and the risk for falls.

C) Interpretation and potential mechanisms of action associated with study' findings

The implications of OA and TKR are discussed thoroughly in the Literature Review (please see Chapter 2 for details). Patients in the current study demonstrated marked improvements in locomotor activity, pain, balance ability, proprioceptive accuracy, and muscular strength after the therapy programme, with greater benefits being apparent in the ESMET group. The SMT's efficacy may be driven by aspects of its content and dosage. It offers an emphasis on functional weight-bearing and balance/agility exercises in its content rather than standardised muscle stretching and strengthening exercises within usual care.

In the current study, substituting a time-matched novel formulation of sensori-motor stimuli, based on precedence (Fitzgerald *et al*, 2011; Riemann, 2002), for conventional exercises using elastic bands or weights for muscle strengthening, facilitated enhanced gains in functional and mechanistic proprioception capacities. Patients were challenged with managing body-mass-related momentum' changes during activities such as step-ups, squats, lateral steps, and obstacle-avoidance to progressively encourage use of vertical ground reaction forces (Farquhar *et al*, 2008), postural balance (Gauchard *et al*, 2010) and excitation of peripheral joint somato-sensory receptors by multi-directional force-stimuli (Behm *et al*, 2002). In this way, vertical ground reaction forces in the knee joint, known to be limited in the first months after surgery (Farquhar *et al*, 2008), can promote more normalised movement patterns and therefore, functional stability and strengthening. Moreover, exercises involving a single limb stance, unstable surfaces, and backward-walking, provide stimuli to knee somato-sensory receptors, mostly of soft tissue origin (since joint receptors have been resected), and challenge balance and proprioceptive acuity not only in the knee but in the peripheral joints as well (Gauchard *et al*, 2010).

Improvement of sensory and motor function induces achievement of improved postural performance (Gauchard *et al*, 2010). Neuromuscular control has been found to be most effectively targeted and improved with the use of the aforementioned elements (Fitzgerald *et al*, 2011; Rienman *et al*, 2002). Consequently, it might have been reasonable to have expected for the ESMET group to demonstrate improved performance and gains compared to the FET group

Superior gains in sensori-motor performance capabilities for the ESMET group compared to control, which had been most pronounced for the operated leg, offered an insight into the mechanisms, by which concomitant improvements in functional and sensori-motor performance were achieved in the current study. These gains may represent normal neurological responses to training in legs residing at lower pre-surgery levels of conditioning capacity status, interacting with the surgical advantages of knee replacement (including normalisation of joint space, release of tight ligaments and capsule, and improved tissue re-alignment and joint sensation) (Heiberg *et al*, 2010). Pohl *et al* (2015) had been unable to detect significant gains in proprioception after implementing sensori-motor training but had presented evidence from patients undergoing both knee and hip replacement surgeries, a much shorter duration of training (three weeks) and some sensori-motor exercises in non-weight bearing positions via a sling system.

Moreover, equivalent gains (~25 %) in muscle strength for both the operated and non-operated legs elicited by SMT represent normal neurophysiological responses to training. Even with the potential intrusion of the physiological effects of AMI, there would appear to be no substantive impediment to the potential for patients to gain strength after TKR surgery. Improvement in muscular strength has been shown to offer better neuromuscular control and locomotor functional ability (Mizner *et al*, 2005; Rienmann *et al*, 2002). This is due to the greater muscular forces and efficiency with which functional tasks can be performed. Patients may demonstrate greater forces for the quadriceps' muscle within the time-frame of rehabilitation and follow-up, due to reduction in pain, joint effusion and arthrogenic inhibition associated with knee OA and acute surgery. Moreover, stronger muscles offer increased functional stability during ADL activities, perhaps due to more efficient muscle activation' patterns. For example, while it's expected that specific high intensity strength training initiated early following surgery (within two weeks) would

have been capable of eliciting quadriceps muscle' strength improvements of 7 % and 30 % at 12 and 26 weeks post-TKR in the operated limb, respectively (Bade *et al*, 2011), evidence from the current and previous (Fitzgerald *et al*, 2011; Ahmed, 2011) studies show that SMT appears to offer some of the training stimuli necessary for potent gains in strength when delivered early after surgery, is perhaps more revelatory. Thus, probably the intensity and dose of studies implementing usual care programmes that typically offer greater emphases on strength conditioning, are amongst the reasons of why they report being incapable of reversing strength loss for up to six months post-surgery (Mizner *et al*, 2005a, b). In the current study, the ESMET group also showed concomitantly superior gains (~50%) in integrated EMG-derived outcomes (peak amplitude and RMS) that were more prominent for the operated leg. The latter suggested an expected physiological coupling of changes amongst indirect (muscle activation) and direct (muscle strength) measures of neuromuscular performance capability. Although there is a relationship between EMG-amplitude and muscle force (especially within isometric conditions of muscular activation, as implemented in the current study), the two indices are not always linearly related. The presence of electric potential differences in a muscle is the result of motor unit action potentials produced by the CNS. Improved EMG activity is attributed to better motor unit activity and better motor unit firing frequency (the neural drive to that muscle group has increased). Therefore, the increase in PF measured in dynamometry with concomitant increases in EMG activity, could be interpreted as increased neural drive to the quadriceps elicited by SMT conditioning. However, no significant relationships were noted amongst change scores for indices of peak force and the EMG-derived outcomes over the 14 weeks of the ESMET programme ($p > 0.05$), which suggested that other factors had been important for determining gains in muscle strength. This interpretation, although plausible, has to be offered with some caution, as a number of factors such as blood flow in the muscle, depth of active muscle fibres within the muscle, cross-talk from other muscles, may also be implicated (De Luca, 1997). Moreover, when muscles are lengthened or shortened, this seems to alter the cross-sectional area of the muscle fibre, which probably changes muscle conduction velocity (Kamen & Caldwell, 1996) and may also change the geometry of the particular region of the muscle being measured during the muscle action. Muscle fibre' composition will affect the relationship i.e. when the faster twitch muscle fibres (for want of a better general term) start activating later in the contraction.

The commonality amongst the extent of SMT-related changes for estimates of strength and neural drive extends further to encompass those for muscle architectural parameters. Using real-time ultrasound to assess muscle architecture' parameters of TKR patients, superior gains (~27 %) were noted for CSA_{RF} during the contracted state at 60 ° of knee flexion for the experimental compared to the control group. The latter effect was more pronounced for the operated limb. This study's CSA_{RF} changes were observed in both relaxed and contracted muscular states, which and endorse the potential importance of SMT to gaining muscle size. The patterns of SMT-related adaptations in performance for strength, activation and muscle size showed some concordance amongst the effect sizes. Nevertheless, a lack of correlation ($p > 0.05$) amongst the change scores for these outcomes suggested that primary determinants for the gains in the ESMET group's strength would not be clearly defined.

Increased muscle' force-generating capability can be achieved by two means. The first is by means of central nervous system' adaptation, whereby greater maximum voluntary contraction is produced by the CNS 'learning' and then subsequently, adapting the pattern of excitation (Rutherford & Jones, 1986). Thus, the force gains are achieved by greater and more effective recruitment of muscle fibres. The second means is by building the physical bulk of the muscle to produce a greater force output for the same neural input (Janda *et al*, 1996). Also, increased muscle' force can be explained by a decrease in pain. Pain leads to a decreased activation level of the muscle by means of arthrogenic and autogenic processes (Rice *et al*, 2010). The anticipation of pain causes the patient to guard against over-exertion within their physical activities, and this in turn, aggravates muscle weakness and the potential for concomitant disability. In the current study, improvements in the contractile capability of muscle produced, as well as improvements in the muscle' bulk (through an increase of CSA), were evident. Moreover, gains (i.e. lower pain scores) in the perceived levels of pain being experienced by patients were of statistical and clinical importance. Therefore, all of the aforementioned mechanisms may have contributed by means of an additive process, or within an interaction, to the gains in neuromuscular performance, or to those in functional capability, which had been observed in the current study.

It is appreciated that both groups were responding positively to rehabilitative training, but the mechanisms driving change might have been heterogeneous and conflated if both groups had been subjected to correlation analyses. However, the sample size is too small ($n = 26$) to perhaps be able to appropriately investigate mechanistic changes as wished. The strength of correlations (and thus the limited extent of shared/pooled variance) does not allow any clear indication of direction and thus, some guidance to the mechanism. Furthermore, the patterning of change scores between functional and sensor-motor indices mimic the changes in effect sizes for outcomes, but similarly suffer from weak correlations, which fail to endorse a clearly defined mechanistic pathway. Overall, it is believed that the data in this study for measures of neurophysiology or morphology, do not allow any indication of any difference in the physiological responses to training of TKR clinical populations from those of asymptomatic / normal populations. As such, advice about sensori- or motor aspects of training for the latter population should be mimicked when devising rehabilitative training for patients undergoing TKR.

In summary, as already discussed in Chapter 2 (section 2.6 for details), the mechanism of action of SMT has been shown to be both central and peripheral as the exercises utilised were primarily motor (efferent) tasks, but also have afferent aspects. In order to approach the potential mechanisms of action associated with SMT, morphological (changes in knee form and structure) and neurophysiological (changes in CNS function) assessments leading to functional changes (i.e. changes in physiological activity i.e. postural sway/balance) during the implementation of SMT, are needed (Hupperets *et al*, 2009). Neurophysiological changes in the current study are reflected by changes in indices of sensori-motor (JPE, FE) and neuromuscular performances (PF). The notion for linked patterns of improvement and determining relationships between secondary neurophysiological and primary functional indices of performance finds some corroboration in the modest relationships reported between change scores of TUG and sensori-motor function indices during the ESMET programme in particular. The favourable changes in muscular firing activity as reflected by EMG parameters (peak amplitude and RMS), further support the likelihood that a neurophysiological mechanism facilitates increased strength and functional capabilities. Morphological changes, in the current study are reflected by changes in a selected index of musculoskeletal performance (rectus femoris muscle' CSA). Gains in the rectus femoris muscle' CSA was again

greater for the ESMET group, with an inter-group difference of 30 %. Therefore, it could be speculated that there had been a morphological-induced effect by ESMET programme. The time-frame of follow-up (14 weeks) could be considered adequate for these changes to have occurred by this mechanism, as the literature in the field suggests a minimum of 6 - 8 weeks of training before any morphological changes can be seen (Blazevich *et al*, 2003). However, no correlational relationship was identified between change scores of TUG and muscle' CSA at any stage of the programme. Therefore, it might be seen that a combination of both morphological (i.e. increase in myofibrillar size and number) and neural drive adaptations (i.e. sensory threshold of peripheral mechanoreceptors, gamma-motor neuron muscle spindle function) resulting from specificity of training (learning and coordination) could be assumed, but that the neurophysiological mechanism seems to be more prominent. Adaptations to externally-induced perturbations, introduced during simple tasks (as within SMT) over relatively short periods, with multiple training sessions, lead to progressive motor skill learning (Dayan & Cohen, 2011). These adaptations are plausible through the process of neuroplasticity in the re-organisation in gray matter or 'within a specific region of the brain' (parietofrontal regions), as seen in studies involving fMRI (Dayan & Cohen, 2011; Taubert *et al*, 2010).

The ESMET rehabilitation resulted in equivalent patterns of improvement for both the leg undergoing surgery and for the leg acting as the contralateral control in sensori-motor function and neuromuscular performance. This could be attributed to either a central mechanism influencing both limbs, or potentially to a learning effect in contralateral reflexive activities (Carroll *et al*, 2006). In contrast, the operated leg showed superior gains in musculoskeletal performance (rectus femoris muscle' CSA). This finding could be explained and moderated by the fact that the majority of knee OA patients present with bilateral symptoms and disability. Usually, the orthopedic surgeon selects the knee to be operated on first according to the severity of the condition, and within a few years, the contra-lateral limb is subjected to TKR as well. However, the severity of OA in the non-surgical knee was not assessed. The operated limb may present with improved mechanical properties and joint' sensation following TKR, due to normalisation of joint space, surgical release of tight ligaments and capsule, and tissue re-alignment (Hunt *et al*, 2009). Therefore, although exercises in the current study were addressed towards, and would probably have corrected afferent senses (including pain reduction) within both limbs,

the exercises may have induced an extra and more pronounced improvement within the operated limb.

If one considers the multi-factorial physical and psychosocial nature of knee OA and consequently the implications of TKR to patients, it becomes understandable that determining the relative contribution of these elements to the observed improvement would be difficult. However, while the ESMET programme was targeted to influence specific components of physical performance, a psycho-social influence cannot be precluded. Both groups undertook exercises aimed at improving the physical performance within a home-based environment. Nevertheless, as has been previously discussed in this section of the thesis, clinical and safety precautions associated with the delivery of the novel exercises, meant that amongst the routine and equivalent clinical oversight for both groups, the ESMET group were necessarily offered access to a single weekly session of clinical supervision and guidance for the 'novel' exercises that patients would be undertaking. This period of supervision had been available to both groups during the early part of the home-based rehabilitation programme, but would have been especially important to those patients in the ESMET group because they would be undertaking exercises that were entirely novel to clinical practice, and early during recovery post-TKR. While this process would not have been expected to disrupt the time-matched design for prescribed exercise training within this RCT, as alluded to earlier within this discussion, it had been acknowledged that there might have been the potential for a subtle bias to have intruded associated with social/clinical approbation during these sessions, as patient-therapist interaction have been acknowledged as an influential factor of treatment outcome (O'Keeffe *et al*, 2016). Moreover, since this type of training has been characterised as diversified and fun for patients (Gstoettner *et al*, 2011), it might have represented an additional factor in encouraging further compliance.

However, significant influences on functional and neuromuscular performance capabilities by such psycho-social mechanisms have not been noted elsewhere during the delivery of a similar RCT (Bailey *et al*, 2014). Furthermore, even if such an effect had intruded, it would have be subsumed effectively within the wider and uncontrolled variations associated with error discrepancies during the delivery of the RCT within the real-world setting of a hospital and care provider. The latter would

have been expected to hinder the statistical detection of any experimental effect over and above the background 'noise'/error within the RCT, but since significant hypothesised interactive effects amongst the performance characteristics of the ESMET and FET groups had been noted, it is likely that Type-II error rates had not been excessive in this respect, and it supports the notion that any potential for social/clinical approbation by patients would have contributed negligibly to the RCT's findings.

D) Limitations & clinical implications

Limitations to this study centred on the following aspects of its design and delivery. Despite group' allocation being concealed formally to patients and investigators by means of independent confidential assignment, logistical limitations meant that patients' assessments and instructional sessions were undertaken necessarily by the primary investigator, with the attendant possibility of an inadvertent cueing to group allocation during conversation and a small potential for bias. Patients' compliance with exercise training had been monitored by self-reported diaries rather than by direct evaluation, which may have led to increased heterogeneity amongst patients' dose-responses. Furthermore, progression within training was monitored and evolved according to patients' weekly functional and postural control capabilities but not titrated against specific objectively-measured criteria or milestones during home-based care. Thus, future studies might reveal whether controlling these aspects of programme delivery would have enhanced efficacy. Ultimately, the study's modest sample' size should preclude excessive generalisation of its findings.

The logistical and financial costs of a comprehensively-blinded trial were beyond the scope of this PhD programme of research. While the group allocation was formally concealed to the investigator until after data analysis, to prevent any potential bias, all patients had necessarily been treated and assessed by the same physiotherapist for the duration of their rehabilitation period. All reasonable attempts had been made to blind the physiotherapist to patients' characteristics during their home-based rehabilitation. Nevertheless, it had been impossible to formally ensure absolute concealment in this context. Counteracting this possibility for the intrusion of bias, it could be argued that the excessively busy nature of an NHS environment for care' provision would have inevitably blunted any real possibility of systematic memories

of the physiotherapist about patients contributing to the potential for bias during assessments.

The use of a single centre of clinical care at a renowned public G.R. University Orthopaedic Trust hospital ensured optimal standardisation of care. This might properly be considered an advantage in the context of the delivery of this exploratory and novel trial. However, the ability to extrapolate findings from this study to other NHS environments, joint systems and surgical interventions, would be expected to be limited compared to findings derived from more representative multi-centre trials.

The observation that the TUG Test represents function and physical performance and would be sensitive to changes in performance capabilities of both a group of TKR patients and of an individual patient was the justification for choosing it as the primary outcome measure. However, the enhanced sensori-motor exercise training programme involved more skilled tasks and movements compared to those within the TUG Test, such as change of direction, walking over obstacles, and standing on unstable surfaces. As such, a more sophisticated assessment tool that better reflects the functional nature of the training exercises might offer increased ecological validity and a capability to better detect subtle alterations in patients' performance capability. Future trials should include performance assessments that involve more skilled movements, walking over more complex obstacles, and with changing speeds and directions while walking.

An additional limitation of this novel study is that, although it was theorised that the ESMET programme would increase participants' confidence to safely engage in a more physically active lifestyle, physical activity was not directly measured. Anecdotal observation during the current RCT's implementation supports the need to measure physical activity with objective measures i.e. accelerometer or video.

As shown by the findings of the current study, patients continued to improve even after finishing the first bout of six weeks exercise that included the supervised sessions, up to the final assessment point, at 14 weeks post-TKR. However, it would be important to know how well these improvements are maintained to six months or

even to one year after TKR, when the rehabilitation therapy programme would have finished.

The current study's findings make an impact on clinical practice, as SMT implemented early, within the post-acute phase (2 - 3 weeks post-surgery), seems to be a feasible, safe approach, with no adverse effects noted. The practical implication relies on the early improvements noted in functional, mobility, balance and quadriceps muscle strength, with a reasonable volume of 30 - 45 min of exercise training, for 3 - 5 session per week incorporating focal sensori-motor stimuli. The advantages in rehabilitation could be delivered successfully within an environment of self-managed, home-based care with no additional costs or specific equipment required. This evidence can promote informed decision-making within clinical practice and where appropriate, foster the effective use of enhanced sensori-motor exercise training that mimics this study's experimental intervention. The findings clinically endorse using ESMET as a superior and efficacious mode of rehabilitation following TKR surgery compared to usual care strategies with improvements observed up to 14-weeks post-surgery. However, a recent systematic review and meta-analysis appraising the influence of SMT on TKR patients has shown that the greater effects of this type of training on balance in particular, can be expected to be maintained until at least mid-term (6 -12 months) following surgery (Domiguez-Navaro *et al*, 2018). This suggests that the specific positive effects of SMT within this study might be maintained accordingly further into the care pathway for longer than 14 weeks.

Anecdotally within the author's experience and clinical observations, patients undertaking SMT are able to adjust sooner to ADL challenges with more confidence, with a greater variety of physiological gait patterns and engage competently with more physically active tasks (i.e. dancing or gardening) than patients undertaking usual care. However, both groups, although feeling empowered by the mode of exercise involving self-managed care, would need guidance and instructions especially for the first month in which pain and joint stiffness would have not fully subsided.

In summary, this was a novel RCT that examined whether or not ESMET rehabilitation out-performed FET rehabilitation using outcome measures applicable to the TKR population. The study was limited by finance and was delivered in a busy

NHS physiotherapy department. Therefore, it had not been delivered without some limitations, which were primarily associated with assessor-blinding and a single-centre environment. Nevertheless, the study's findings add to the research underpinning evidence-based medicine and provide a foundation for future research in this area.

On completion of this thesis, its findings and the potential advantages of the ESMET-based rehabilitation will be disseminated to inform clinical practice within orthopaedic hospitals, and ultimately, with further research, to contribute to the debate about whether ESMET's greater efficacy might also contribute to a more cost-effective strategy for TKR patients' rehabilitation. Some of the thesis's findings have already been disseminated within the clinical and scientific literature (four papers have been published or accepted for publication in peer-reviewed clinical journals so far; please see page xviii at the beginning of this thesis, for details). The clinical implication is that ESMET rehabilitation will provide superior gains compared to FET rehabilitation. The thesis's results would give credence to the recommendation that post-operative rehabilitation could ultimately be prescribed with suitable safety, efficacy and effectiveness in an ESMET format, and initiated within two weeks after TKR surgery.

Chapter 9

Thesis summary and conclusion

The research topic of this PhD was prompted by an interest in measuring the impact of targeted SMT rehabilitation-related strategies on TKR populations. A great variability of how patients' QoL was affected by the trends of TKR rehabilitation (with regards to essential components within a rehabilitation programme, time-frame of the delivery of the included components, and of the characteristics of the health-care environment) had been observed (Oatis *et al*, 2014). With ever increasing health-care costs, it is vital that clinicians, and researchers also, become further involved in the field of optimised TKR rehabilitation, understand how to measure patients' deficits and how to efficiently manage any deficits. Therefore, this thesis was designed to make an original contribution to knowledge in relation to whether functional performance within a TKR clinical population is affected by SMT. As outlined in the introduction and background review of this thesis, contemporary rehabilitation programmes following TKR offer improvements (up to 25 % in performance-based TUG vs 70 % in PROMs) in functional performance one year post-surgery (Lowe *et al*, 2007; Mizner *et al*, 2011; Pozzi *et al*, 2013). However, the extent of recovery has not fully reached patients' expectations (Choi & Yong, 2016; Kim *et al*, 2009; Nillsdotter *et al*, 2009). The percentage of patients experiencing persistent pain is high, accounting for approximately 30 % and the reported incidence of residual symptoms and functional problems ranging from 33 % to 54 % at one year after surgery (Nam *et al*, 2014). Therefore, in order for the locomotor performance in the early stage after TKR to reach the pre-operative level of locomotor function at least four to six months are necessary, and relevant deficits are still present one year after TKR. Moreover, residual deficits in balance performance, neuromuscular control, muscle strength have been reported in patients following TKR (as discussed in Chapter 2). A battery of tools with good clinimetric properties (discussed in Chapter 3) recording relevant performance objectively or self-perceived have been proposed for this clinical population. No specific guidelines exist as to what should be the content of rehabilitation.

For this purpose, a survey was designed to pragmatically describe according to physiotherapists' views the current clinical practice in terms of content, environment and timeline in Greece for patients undergoing TKR. The findings from the survey (Chapter 4) showed three main aspects: (1) while a variety of rehabilitation strategies are being used during clinical care management in Greece, there is a common context of rehabilitation that constitute usual care which focused on

predominantly on muscle strengthening, knee ROM and functional training; (2) patients were usually discharged with a suggested exercise programme that was delivered within a home-based environment with minimal or no supervision and this was pragmatically the option of care most frequently used, 3) physiotherapists indicated that they did not regularly use specific outcome measures, and within those most commonly encountered were the VAS, TUG and goniometry, obviously based on familiarity and clinical utility. There was a discrepancy whether balance components are essential within TKR rehabilitation and if yes, when is the appropriate time to initiate them. No optimal way was suggested on the dose of exercise that should be implemented. Duration of training lasted for approximately six weeks post-surgery. So far, findings encourage direct discharge to home-based rehabilitation as a rationale use of resources and a viable option for many patients (Froimson, 2013; Chimenti & Ingersoll, 2007; Roos, 2003).

Within less than a decade rehabilitation programmes have sought novel components to mitigate patients' deficits. One year after TKR a strong correlation has been reported between improved quality of life (SF-36) and several measures of static and dynamic balance (Schwartz *et al*, 2012). Therefore, it has been possible to show for the first time that balance performance may have a significant influence on the outcome of TKR. According to the author's knowledge only pilot clinical trials carried out previously have reported the feasibility of introducing sensori-motor components following surgery (Piva *et al*, 2010). For this purpose, two systematic reviews (Chapter 5 and 6) and one clinical trial (Chapter 8) were designed in parallel with the aims to address specific questions given below:

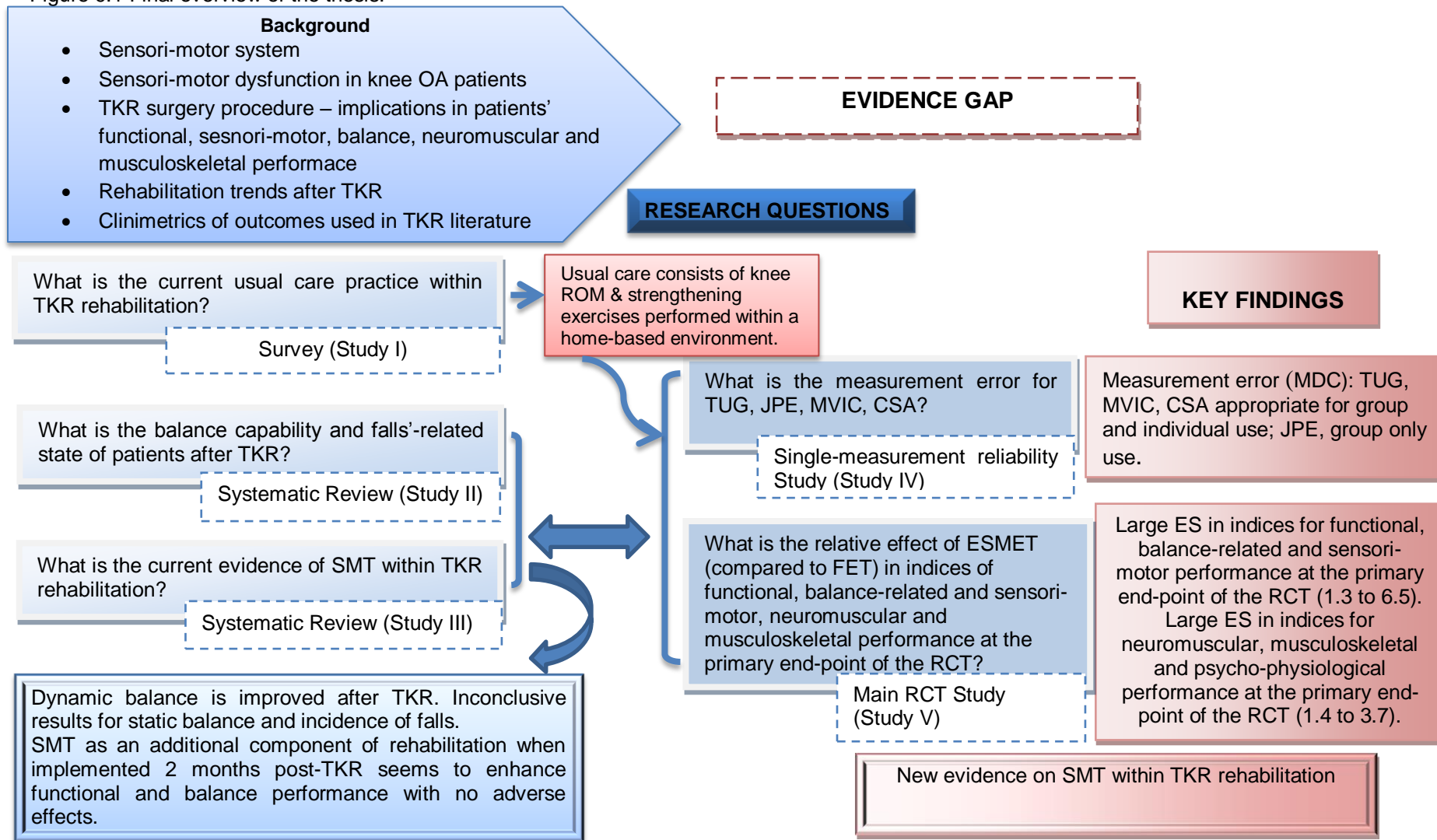
- What are the effects of TKR on balance and incidence of falls in patients with knee osteoarthritis following total knee replacement by systematically reviewing the available literature (Chapter 4; Moutzouri *et al*, 2016c)?
- What are the effects of SMT on balance and functional performance in patients following TKR, through a systematic review of the literature (Chapter 5; Moutzouri *et al*, 2016a)?
- What is the single-measurement reliability and reproducibility of the selected battery of indices (for the main study) related to functional, sensori-motor,

neuromuscular and musculoskeletal performance in a clinical population of patients undergoing TKR?

□ What is the effect of training enhanced with novel sensori-motor elements in indices of functional, balance-related, sensori-motor, neuromuscular, musculoskeletal and psychophysiological performance in patients following TKR (Moutzouri *et al*, 2017)? Moreover, whether the underlying mechanisms of SMT local or more central, was indirectly examined.

An overview of the thesis, visually presenting the relationship between the research questions and how 'gaps' in the current evidence were addressed, is presented in Figure 9.1. The purpose of this Chapter was to summarise and synthesise findings of the aforementioned studies in the context of the existing literature. This chapter will consider the limitations of the studies and discuss the implications of these observations for future research.

Figure 9.1 Final overview of the thesis.



What are the effects of TKR on balance and incidence of falls in patients with knee osteoarthritis following total knee replacement (a systematic review)?

This first systematic included 14 studies (Level of Evidence II-IV) with a total sample of 687 patients (167 controls). The findings of this systematic review provide moderate evidence to support that TKR influences dynamic balance positively (up to 37 %) for up to one year following surgery. Inconclusive are the findings amongst studies regarding static balance (10 % - 60 %). However, both static and dynamic balance (in the frontal plane) remains impaired compared to age-matched controls. Moreover, indefinite are the findings as to whether people after TKR actually report reduced or the same number of falls (Level of evidence II-IV). The incidence of falls (40 % - 48 %) remains higher than that of community age-matched controls (30 % - 33 %). Total knee replacement influences positively the incidence of falls by switching 54.2 % of pre-operative fallers to post-operative non-fallers. Therefore, clinicians could expect improvements in patients dynamic balance following TKR, but there are still considerable deficits in balance performance that risk safe mobility and should be addressed with targeted rehabilitation. However, findings of this systematic review are limited by the moderate methodological quality of included studies and therefore generalisation of findings should be made with caution.

As this was the first systematic review in the field, broad inclusion criteria were used for study selection. In a future relevant study, the systematic review should include only studies incorporating a control group and the OA patient group being compared and followed up with their post-TKR state (and not just the TKR patient group compared with age-matched controls). An emphasis among studies incorporating different TKR surgery techniques in response to balance and falls incidence could be of clinical relevance. Moreover, a division between studies implementing no physiotherapy programme post-surgery and studies incorporating studies with usual care programmes could also be a future consideration.

What are the effects of SMT on balance and functional performance in patients following TKR (a systematic review)?

This first systematic included five RCT studies (Level of Evidence II) with a total sample of 371 patients (184 controls) investigating the effects of SMT in TKR

patients' functional and balance performance. The findings of this systematic review provide robust evidence (IIa) (5-7 PEDro score) with three (out of five) study' findings supporting the addition of SMT into usual care programmes. The practical implication relies on the improvements on balance performance with the supplementary SMT on the usual functional care programme. Sensori-motor training implemented for 6 - 8 weeks and initiated two weeks post-TKR, may be effective and tolerated well by patients, with no fear of adverse effects in physical function.

The robustness of the conclusions about effectiveness and optimal volume of training however, need necessarily to be tempered against substantial differences in methodological design (including time-line of rehabilitation, volume of exercise, and the type of sensori-motor training' components) amongst the studies that had been available for inclusion. Furthermore, most of the reviewed studies had relied on additional duration of sensori-motor training compared usual practice to deliver effectiveness, and thus hindering the ability to attribute gains solely to the focal sensori-motor training (Moutzouri *et al*, 2016a). Finally, a lack of acceptable effect size in some studies, combined with underpowered experimental designs, suggested either the possibility of either a lack of potency of intervention or a compromised capability to detect subtle gains that might have been offered by the intervention. Both aspects threaten what might be generalised from the findings in this population. A relevant systematic review and meta-analysis published in 2018 by Dominguez-Navaro appraised the effects of SMT when included in the methods of standard physiotherapy care for patients undergoing total hip or knee replacement. Findings are in agreement with the current study supporting the effects of SMT in enhancing the early postoperative outcomes after TKR over the standard procedures in terms of balance and self-reported functionality. The follow-up evaluations confirmed that the effects were maintained at mid-term in terms of gains in balance.

Overall, the results from the main thesis' study, in conjunction with a recent study by Jogi *et al* (2015), support the early initiation of enhanced sensori-motor exercise training with 2 - 3 weeks post-surgery with no adverse effects to patients. Similarly, the superior improvements in functional and sensori-motor performance for the ESMET (compared to control) suggest that an effective mode of practice with a reasonable volume of training (~five sessions per week; 35 to 45 minutes per

session; 12-week programme) can be achieved by incorporating components of SMT within, rather than in addition to, contemporary functional exercise programmes of patients undergoing TKR. Thus, conclusions within the recent systematic review (Moutzouri *et al*, 2016a) might usefully be modified to take account of this emerging evidence for optimised timing, context and duration of enhanced sensori-motor exercise training within rehabilitative programmes. Interestingly, a recent study by Pohl *et al* (2015) suggested that altering the frequency of the delivery of sensori-motor stimuli may not necessarily be a significant determinant of optimised neurological gains during exercise training.

As this was the first systematic review in the field, again broad inclusion criteria were used for study selection. The capability to generalise from findings is limited due to the small number of included studies (five) and the diversity of environments and time-line of rehabilitation offered in the relevant study' protocols. In a future relevant study, a systematic review should include only RCTs implementing SMT post-operatively within land-based environments. As the surgical procedure greatly affects the sensori-motor system, even when the PCL is preserved, the maintenance of improvements after surgery owing to pre-operative training are limited. An emphasis on dose-response effects with a potential meta-analysis should be considered to monitor the effects of intensity and frequency of exercise during training.

What is the single-measurement reliability and reproducibility of the selected battery of indices (for the main study) related to functional, sensori-motor, neuromuscular and musculoskeletal performance in a clinical population of patients undergoing TKR?

The rationale for undertaking this study was to confirm and report the level of reproducibility and limits of measurement precision of selected indices to address the aims of the main study, acquired by the principal investigator during data collection. Indices of functional (TUG), neuromuscular (PF) and musculoskeletal performance (CSA_{RF}) showed excellent levels of single-measurement reliability (ICC > 0.80). On this basis, these indices can be recommended for use within group-based experimental designs and at the level of an individual patient. Clinicians working with patients undergoing TKR could trust the index of functional mobility

(TUG Test) and quadriceps muscle strength measure (PF), as measured via the MVIC technique, to detect responses to rehabilitation. However, indices of sensori-motor performance showed acceptable levels of reliability close to 0.70 (ICC: 0.60 - 0.83). Measurement precision of the JPE indices that have been considered, offer sufficient measurement reproducibility (for both operated and non-operated limbs), for them to be reasonably recommended for use in the main RCT study (group-based design) to demonstrate potential efficacy of training programmes. Furthermore, changes in patients' performance capabilities that exceed the confidence limits associated with MDCs and corresponding CV %, identified within this study, will show real effects during the clinical assessments of individual patients undergoing TKR surgery. More specifically, a change of at least ± 1.7 s is required on the performance of the TUG Test, in order to demonstrate a real change in the functional ability of an individual patient, or in a wider context, of the group mean capability of a TKR population. A change of at least ± 8.6 N on scores for PF is required to demonstrate a real change in the knee extensors neuromuscular performance of an individual patient undergoing TKR. A change of at least 20.4° is required during the assessment of JPE to demonstrate a real change in the sensori-motor responses. Similarly, a change of 35.6 mm^2 in the rectus femoris muscle' CSA is required to demonstrate a real change in musculoskeletal performance. However, the results of this reproducibility and single-measurement reliability study was carried out on a relatively small group of patients undergoing TKR, and therefore findings cannot be generalised without caution to the TKR clinical population. A future study designed to address this study' aims should include a larger sample followed up by at least two researchers (to examine inter-tester reliability as well) in shorter time intervals (within ten days) between measurements. Another interesting perspective for responsiveness of indices would be whether they could discriminate amongst fallers and non-fallers.

What is the effect of training enhanced with novel sensori-motor elements in indices of functional, balance-related, sensori-motor, neuromuscular, musculoskeletal and psychophysiological performance in patients following TKR?

The findings of the current study (scored as 6/10 in PEDro) showed that a 12-week SMT programme initiated within ~2 weeks post-TKR in a home-based environment

was superior to a time-matched usual care programme in terms of patients functional, balance-related, sensori-motor performance (ES: 1.3 - 2.8 compared to 0.3 - 1.4). Direct (quadriceps' muscle strength) and indirect (EMG-derived measures from RF) indices of neuromuscular capacity, as well as measures of muscle size (CSA_{RF}) showed statistically significant greater improvement for the group undertaking SMT compared to the group undertaking usual care (ES: 1.5 – 3.7 compared to 0.7 – 2.7). Knee ROM showed statistically significant but not clinically significant greater improvement for knee flexion for the experimental group compared to control, but no difference for knee extension ROM between groups. Clinically important greater improvement (indicated by relevant MCIDs), as captured by self-reported indices of functional performance and QoL, was again showed for the group undertaking SMT compared to control (ES: 3.8 - 6.2 compared to 1.2-2.8). Interestingly, but in accordance with relevant literature, the magnitude of improvement was revealed greater by PROMs than that revealed by performance-based measures, probably due to pain subsiding. Limitations that should be taken under consideration when interpreting findings are the single-blind design and the potential effect of therapist interaction intruding within the experimental group. A statistically significant greater self-reported compliance with exercise was found when patients diaries were analysed, with the ESMET group reporting a ~10 % higher compliance. Therefore, although it is not supported by the literature (Coppola *et al*, 2008; Bailey *et al*, 2014; Pesavento *et al*, 2017) a psychosocial effect due to the greater interaction with the therapist may have intruded in the study' findings.

A future study would include double-blinded design with a large sample where different levels of dose and interaction could be examined. Moreover, future research should include the setting of objective criteria for patients' progression within SMT and the individualised titration of exercise intensity for optimised dose-responses. More specifically, the cohort would be divided into three arms of a 12-week SMT group. Each arm would be split into two groups according to the level of therapist-interaction, i.e. one with minimal and one with no interaction. The first arm would be undertaking SMT twice a week for ~40 min, the second arm would be undertaking SMT three times per week for 25 min and the third arm would be undertaking five times per week for 15 min. Patient follow-up would be intended at least mid-term, for six months after training.

This thesis provides evidence that both the FET rehabilitation and the intervention under investigation, ESMET, were efficacious for TKR rehabilitation. Both methods elicit improvements in functional and physical performance capacities when measured by both performance-based indices and PROMs. Both approaches to rehabilitation seem to have provided improvements in both the operated and non-operated limbs. However, results showed that ESMET rehabilitation was superior, providing in most outcomes, a 30 % to 50 % advantage compared to the gains delivered by FET. Thus, in an albeit modestly-sized sample of patients undergoing total knee replacement, the same prescribed duration of rehabilitative training has yielded significant improvements in almost all outcomes. While minimally-important clinical differences (Sloman *et al*, 2016) for outcomes remain typically elusive in this clinical population (Keurentjes *et al*, 2016), the extent of the gains favouring enhanced sensori-motor enhanced exercise training suggest that they are likely to be relevant clinically, and that the findings warrant further verification in subsequent well-controlled clinical trials. This novel finding was in agreement with the prevailing opinion from a very small volume of relevant literature investigating the potential of the use of sensori-motor training when it has been added to the usual care involving a functional training programme.

As indicated by the Background Chapter (Chapter 2) patients' functional performance is reported to decline by 15 % (40 % in muscle strength) in the first month after surgery and to improve with usual care rehabilitation by 25 % one year post-TKR (Mizner *et al*, 2011). Dynamic balance performance is reported to improve up to 37 % after TKR. However, as indicated by the current study and studies using SMT (Dominguez-Navaro *et al*, 2017; Doma *et al*, 2018), the interaction and/or addition of surgery effects and SMT rehabilitation offers 30 % - 50 % greater improvements in functional and balance performance than usual care. However, interpretation of findings needs to be made with caution due to the aforementioned limitations of the current study.

The clinical implications are that early (2 - 3 weeks post-surgery) implementation of focal sensori-motor stimuli incorporated within the functional training programme could offer early improvements in functional, mobility, balance and quadriceps muscle strength. A reasonable volume of 30 - 45 min of exercise training, for 3 - 5 sessions per week could be delivered successfully, with minimal supervision, within

an environment of self-managed, home-based care with no additional costs or specific equipment required. Moreover, since a calibration amongst the subjective and objective indices has not been found, it is suggested for clinicians to use both (preferably TUG, overall stability index, quadriceps peak force and a self-reported measure of knee-related functional performance, such as KOOS or KOS-ADL) to capture responses to SMT. This evidence can promote informed decision-making within clinical practice and where appropriate, foster the effective use of enhanced sensori-motor exercise training that mimics this study's experimental intervention compared to usual care strategies. However, improvements could not be ensured further than the 14-weeks post-surgery, where the end-point of final assessment was.

Moreover, could underlying mechanisms of SMT (local or more central) be indirectly extrapolated?

In order to indirectly approach the potential mechanisms of action associated with SMT, morphological (changes in knee form and structure) and neurophysiological (changes in CNS function) assessments leading to functional changes (i.e. changes in physiological activity i.e. postural sway/balance) during the implementation of SMT, are needed (Hupperets *et al*, 2009). Neurophysiological changes in the current study, as reflected by gains in indices of sensori-motor (JPE, FE) and neuromuscular performances (PF, EMG-derived measures), support the likelihood that a neurophysiological mechanism facilitates increased strength and functional capabilities. Moreover, a 30 % increase in rectus femoris CSA for the ESMET group also shows morphological gains. Therefore, it might be seen that a combination of both morphological (i.e. increase in myofibrillar size and number) and neural drive adaptations (i.e. sensory threshold of peripheral mechanoreceptors, gamma-motor neuron muscle spindle function) resulting from specificity of training (learning and coordination) could be assumed, but that the neurophysiological mechanism seems to be more prominent. However, linked patterns of improvements amongst relevant indices were not supported as only weak or no correlations were revealed.

Limitations and overall future recommendations

Limitations to this study centred on the following aspects of its design and delivery. Despite group' allocation being concealed formally to patients and investigators by

means of independent confidential assignment, logistical limitations meant that patients' assessments were undertaken necessarily by an investigator, with the attendant possibility of an inadvertent cueing to group allocation during conversation and a small potential for bias. Patients' compliance with exercise training had been monitored by self-reported diaries rather than by direct evaluation, which may have led to increased heterogeneity amongst patients' dose-responses. Furthermore, progression within training was monitored and evolved according to patients' weekly functional and postural control capabilities but not titrated against specific objectively-measured criteria or milestones during home-based care. Thus, future studies might reveal whether controlling these aspects of programme delivery would have enhanced efficacy. Ultimately, the study's modest sample size should preclude excessive generalisation of its findings.

Future research should include the setting of objective criteria for patients' progression within SMT and the individualised titration of exercise intensity for optimised dose-responses. Moreover, future studies might indeed consider delivery of ESMET within a multi-centre comparison to confirm the wider applicability of this study's exploratory findings. The process of designing a multi-centre trial that includes formal measurements of adherence to the prescribed 'volume' and 'intensity' of exercise, together with objective monitoring of ADLs, might offer more effective dose-response characteristics within the patients' programme of training and therefore, offer an enhanced potency for the ESMET intervention. Additionally, it might be advisable that future research investigates the longer-term outcomes and potential falls' rates following ESMET rehabilitation in a more systematic manner compared to that offered in the current study (i.e. patient-reported falls over the follow-up period of just 14 weeks). Finally, future studies should also consider the calibration amongst substantive physical gains and any patient-perceived changes in physical capability, especially in self-managed care environments.

Conclusions

The majority of patients (~70 %) following TKR surgery experience substantial pain relief. However, their functional capabilities, muscle strength (Chapter 2) and balance performance (Chapter 5) although improved, remain substantially impaired. Contemporary clinical practice contains considerable variability in timing of delivery, utilisation of clinical resources and in exercise content. Nevertheless, delivery of

exercise within home-based environments, with a predominant focus on knee ROM and muscle strengthening exercises, seems to be the most frequent option of care (Chapter 4). Evidence from the thesis (Chapter 3) allows the conclusion that a battery of outcome measures, with functional, neuromuscular and sensori-motor focus, with acceptable clinimetric properties, have been suggested for use in the clinical practice of patients following TKR. However, no specific outcome measures or criteria had achieved a predominance of reported use by physiotherapists for assessing patients' functional performance or guiding exercise progression. Therefore, patients' full potential for optimal responses to exercise-based rehabilitation has not been exploited (Chapter 3 & 4). This thesis facilitates conclusions to be drawn about the efficacy of targeted approaches based on sensori-motor training, for mitigating patients' remnant impairments (Chapter 6).

In summary and in accordance with emerging evidence from the systematic review (Chapter 6) and the relevant contemporary literature, the current study's findings endorse using the enhanced sensori-motor training as a superior and efficacious mode of rehabilitation following TKR surgery compared to a time-matched usual care programme. The novel exercise programme was delivered successfully: a) within an environment of self-managed, home-based care, b) soon after surgery (2 - 3 weeks post-surgery), and c) involved an increased proportion of exercise focusing on improving sensori-motor function integrated with a time-matched prescription of functional rehabilitative exercise (Chapter 8). This evidence can promote informed decision-making within clinical practice and where appropriate, foster the effective use of enhanced sensori-motor exercise training that mimics this study's experimental intervention. The greater magnitude of improvements in functional mobility, sensori-motor and neuromuscular performance for enhanced SMT support its use as a more beneficial rehabilitative approach compared to functional exercise training, compared to functional exercise training at short-term (14 weeks post-surgery). Nevertheless, this study employed a modestly-sample size, which precluded excessive generalisation of findings. A potential for bias in the results cannot be excluded due to the study's single-blind design and the minimal extra level of supervision offered to patients within the ESMET group to ensure the safe delivery of the novel elements of SMT (Chapter 8). By investigating the possibility of improved beneficial gains by rehabilitating using a novel ESMET format and a time-matched prescription of therapy, this study offers unique findings for patients

undergoing TKR. Although not tested formally for cost-effectiveness, the findings from this thesis suggest that the protocols for the delivery of ESMET-based rehabilitation might be applied immediately within a clinical setting, without any apparent extra cost. Further research to understand the cost-effectiveness of the ESMET would help to support the use of this intervention to enhance health care delivery. Since, mounting evidence (from 2010 till present) is suggesting that SMT is considerably impacting positively on TKR patients' functional and balance performance then, it is recommended that future research should explore the dose-response effects of SMT. Evidence of independence amongst outcome measures from the thesis allows the conclusion that clinical guidance on rehabilitative progression and on when patients might potentially return to full function safely is likely to be achieved prudently by deploying a battery of PROMs and multi-faceted performance-based measures reflecting functional, balance and muscle strength performance (Chapter 7 & 8). The latter would be preferable to using and relying upon data from any single outcome measure. Based on the evidence from current experimental study and from the relevant contemporary literature, it seems that performance-based measures of muscle strength and functional capability are capable of detecting actual gains elicited by rehabilitative training with most precision, (Chapter 7 & 8).

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Appendices

Appendix I: Survey Questionnaire

CURRENT PHYSIOTHERAPY PRACTICE AFTER TOTAL KNEE REPLACEMENT

If you are completing this survey on-line, please ensure your RESPONSES are NOT IN BOLD

1. What does the in-patient acute care physiotherapy intervention involve?
(NA if knee replacement surgery not undertaken)

2. How many days is patients' Length-of-stay routinely in TKR?

- a. 1-3
- b. 3-5
- c. 5-8
- d. >8

3. What are the discharge criteria from physiotherapy in the acute care phase?
(NA if knee replacement surgery not undertaken)

4. Do you: (underline all applicable)

- a. Routinely refer your patients to out-patient physiotherapy
- b. Routinely refer your patients to an in-patient rehabilitation facility or ward
- c. Only refer to either of the above if rehabilitation is considered necessary.
Please specify indications for rehabilitation if (c).

5. What mode of rehab does your hospital/clinic/service provide after discharge from acute care? (underline all applicable)

- a. Inpatient rehabilitation (in specific rehab ward)
- b. BASIC Home programme (exercise sheet and advice only)
- c. MONITORED Home programme
- d. One-to-one treatment
- e. Land-based supervised exercise classes (usual class size: _____)
- f. Water-based supervised exercise classes (usual class size: _____)
- g. Other -- specify:
- h. None

6. Excluding the BASIC home programme, which of the provided rehab modes do most of your patients receive? (specify one only = primary programme)

7. What post-operative week does this primary programme usually commence? (for patients without complications)

Week _____

8. Please indicate which of the following factors had an impact on the choice of primary programme.

Scale of importance (Very, Moderately, Not at all) Impact on choice (tick) (yes/No)

- a. Established practice/tradition
- b. Surgeon preference
- c. Limited staff resources
(hence home/group programme)
- d. Patient transport difficulties
(hence home programme)
- e. Health insurance re-imburement
- f. Patient preferences
- g. Long waiting list
(hence home/group programme)
- h. Appeared to be associated with
better patient outcomes
- i. Other factors (specify)

9. Which was the most important factor guiding your choice and what are your expected patient' outcomes at 6 weeks post-TKR? Are there any exclusion criteria? (List 3 most important)

For this primary programme:

10. What are your discharge criteria? (List 3 most important)

11. What assessment tools do you employ to measure progression and discharge outcomes?

12. On average, by what post surgery week have most patients been discharged from this programme?

Week _____

If your primary programme is one-to-one treatments...

13. What treatment (s) do you provide (NA if primary intervention is not one-on-one) On average, how many one-on-one sessions does a patient receive per week?

14. Which factors influence the rationale for the TKR programme you are implementing and which residual problem post-surgery do you consider most important ?

15. What type of activities/exercises do you predominantly incorporate?

(underline and specify ONE only, if yes indicate before or after the 6th week post-TKR). **Where is the emphasis in your programme?**

- a) aerobic exercises - specify;
- b) strength exercises - specify;
- c) ROM - specify;
- d) functional tasks - specify;
- e) balance exercises – specify how/when;
- f) all / some above equally – specify

16. What predominantly guides exercise INTENSITY in your programme?

(underline ONE only)

- a) Formal exercise prescription eg Target heart rate, Borg scale for exertion or dyspnea, repetition maximum, number of repetitions
- b) Patient tolerance eg level of pain, informally assessed level of exertion
- c) Intensity not specifically monitored

17. What predominantly guides exercise PROGRESSION in your programme?

(underline ONE only)

- a. patient tolerance
- b. attainment of strength and endurance goals
- c. attainment of functional goals
- d. other - specify.

18. Typical duration of a rehab session?

- a) 0-15 mins;
- b) 16- 30 mins;
- c) 31 - 45 mins;
- d) > 46 mins.

19. What are your expected patient' outcomes at 6-months post-TKR?

20. On average, how many formal sessions of rehab do patients attend per week? What is patients' usual expectation up to discharge? When and why do they usually end the physiotherapy programme?

21. What predominantly guides DISCHARGE from rehab?

(underline ONE only)

- a) Patient- determined;
- b) Therapist-determined;
- c) Objective observer-measured criteria
- d) Waiting list
- e) Other - specify.

22. Does your programme and/or walking aid progression differ according to:

(underline ALL applicable)

- a) Surgeon preference – eg specific protocol
- b) Presence or absence of cement
- c) Patient factors – specify
- d) Other factors – specify

-----///-----

23. Respondents' profile

A)What is your work field:

- 1) public hospital
- 2) private hospital
- 3) Rehabilitation center
- 4) Private Physiotherapy clinic
- 5) Free-Lance Physiotherapist-visit patients at home
- 6) Other please specify

B)Please specify years of clinical experience

- 1) 0-1
- 2) 1-5
- 3) 5-10

4) >10

C) How many TKR patients do you regularly see annually?

D) What is the level of your study?

E) Do you have any specialty in Physiotherapy?

1) Musculoskeletal

2) Orthopaedic

3) Cardio-respiratory

4) Paediatrics

5) Sports

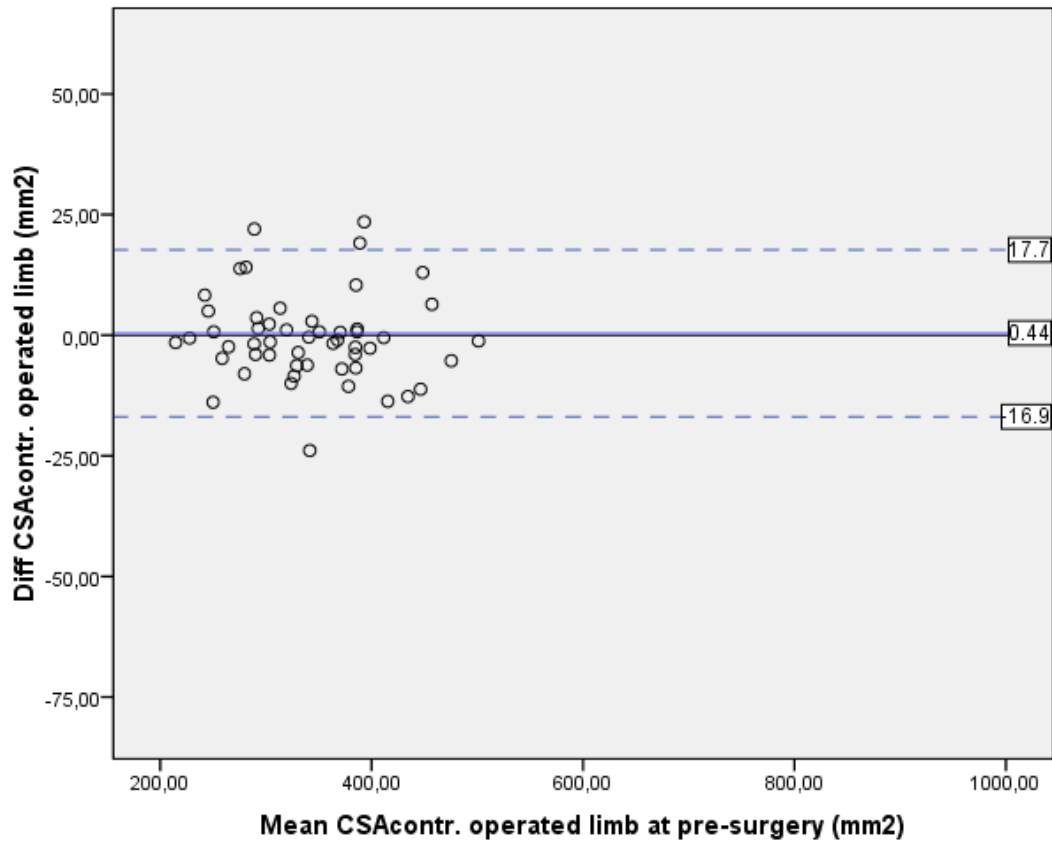
6) Other, please specify

Thank you for your time.

Appendix II:

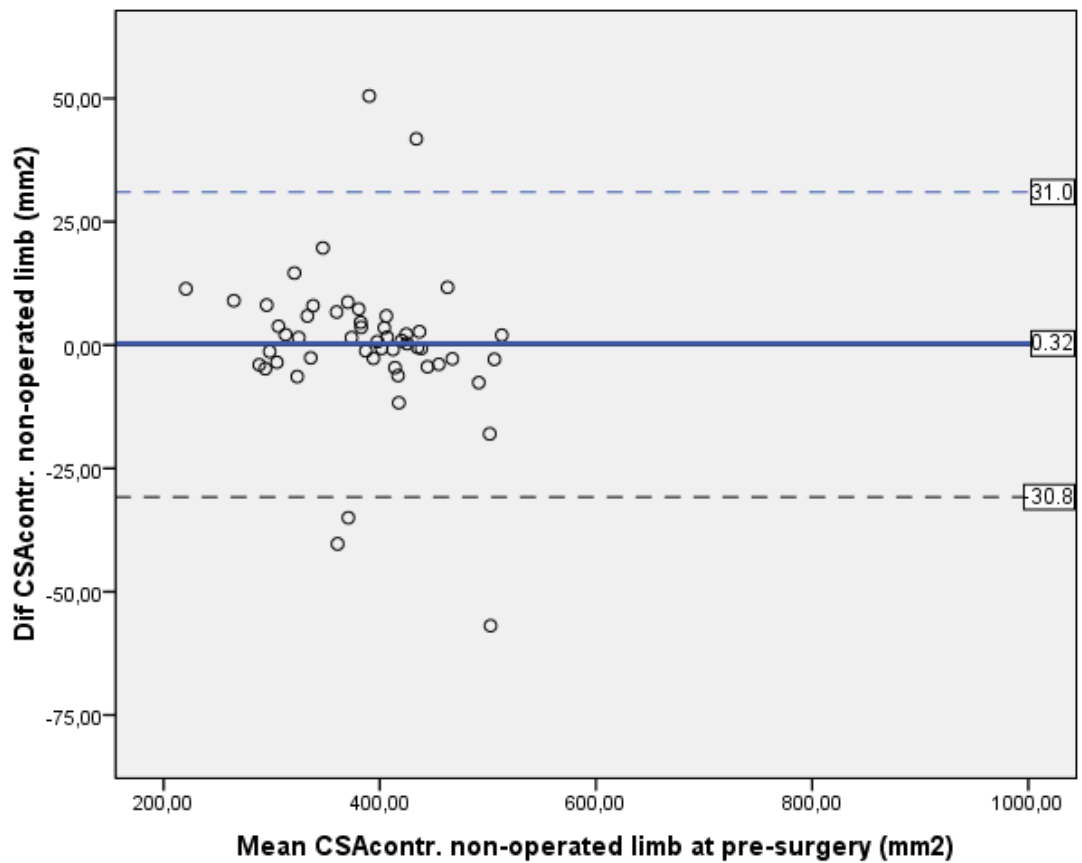
Bland & Altman limits of agreement plots for rectus femoris CSA as part of the single measurement reliability study (Chapter 7), are presented below.

Figure 7. 2a Bland & Altman plot for rectus femoris CSA for the operated limb at pre-surgery (0 weeks).



As depicted by Figure 7.2a, there is large amount of points with almost excellent agreement (data points close to zero). There are 4 outliers, outside the 95% LoA, three above the upper limit and one below the lower limit. There is a small systematic patterning bias towards the first measurement which deviates from zero 0.44mm^2 .

Figure 7. 2b Bland & Altman plot for rectus femoris CSA for the non-operated limb at pre-surgery (0 weeks).



Again in Figure 7.2b, a large amount of patients' data points show very good to excellent agreement and a significant amount of data points are clustered around zero.

Figure 7.2c Bland & Altman plot for rectus femoris CSA for the operated limb at 8 weeks post-TKR.

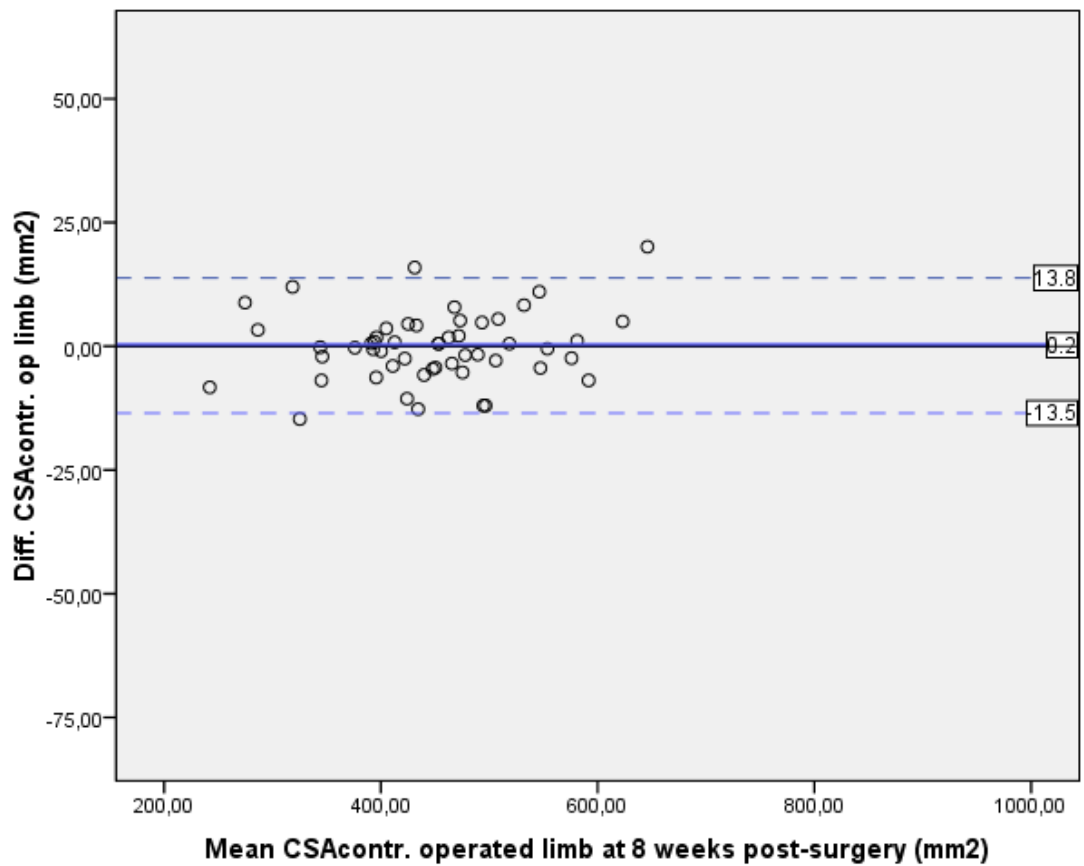
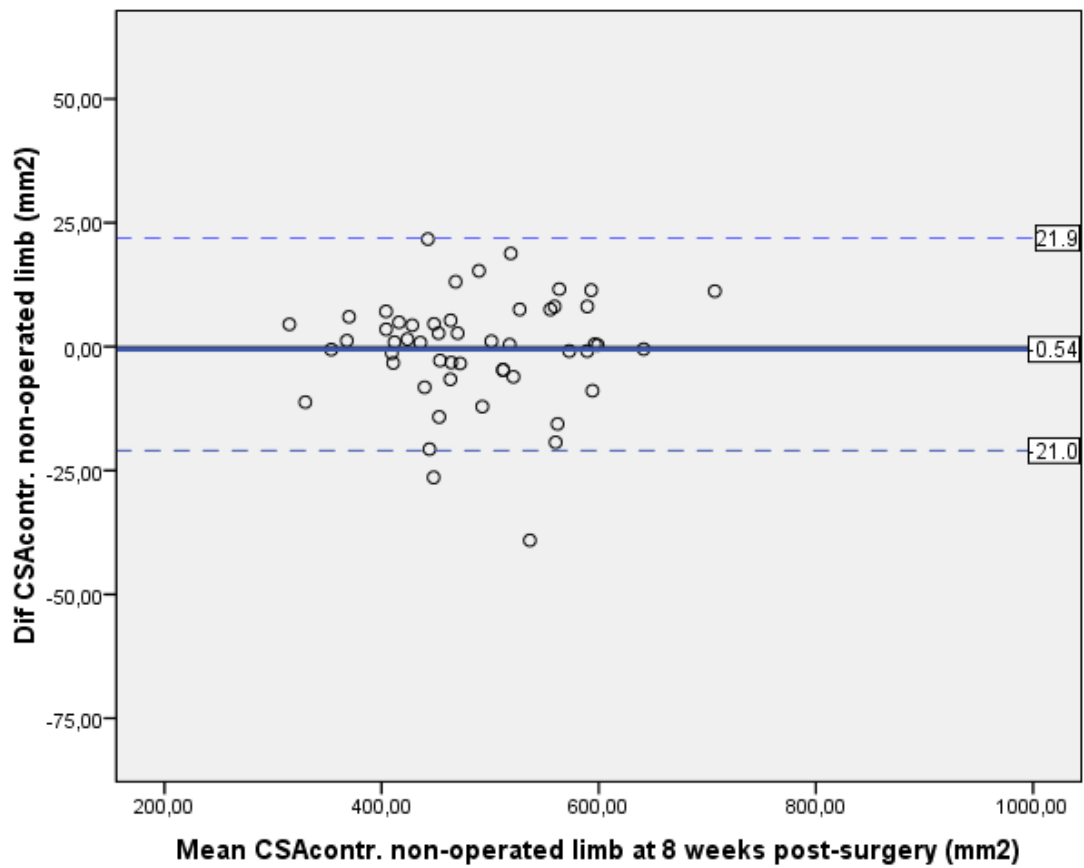


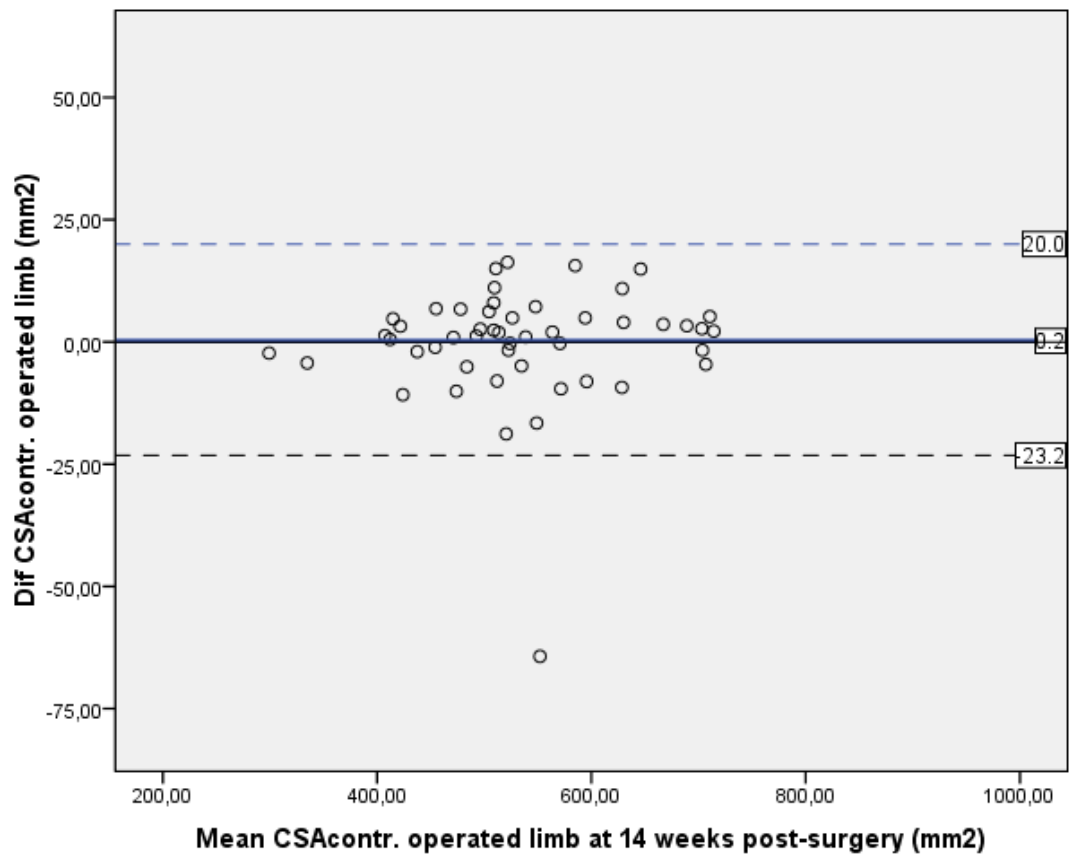
Figure 7.2c, shows that although data points are relatively evenly spread above and below zero, they are largely scattered within 95 % LoAs at 8 weeks post-surgery.

Figure 7.2d Bland & Altman plot for rectus femoris CSA for the non-operated limb at 8 weeks post-TKR.



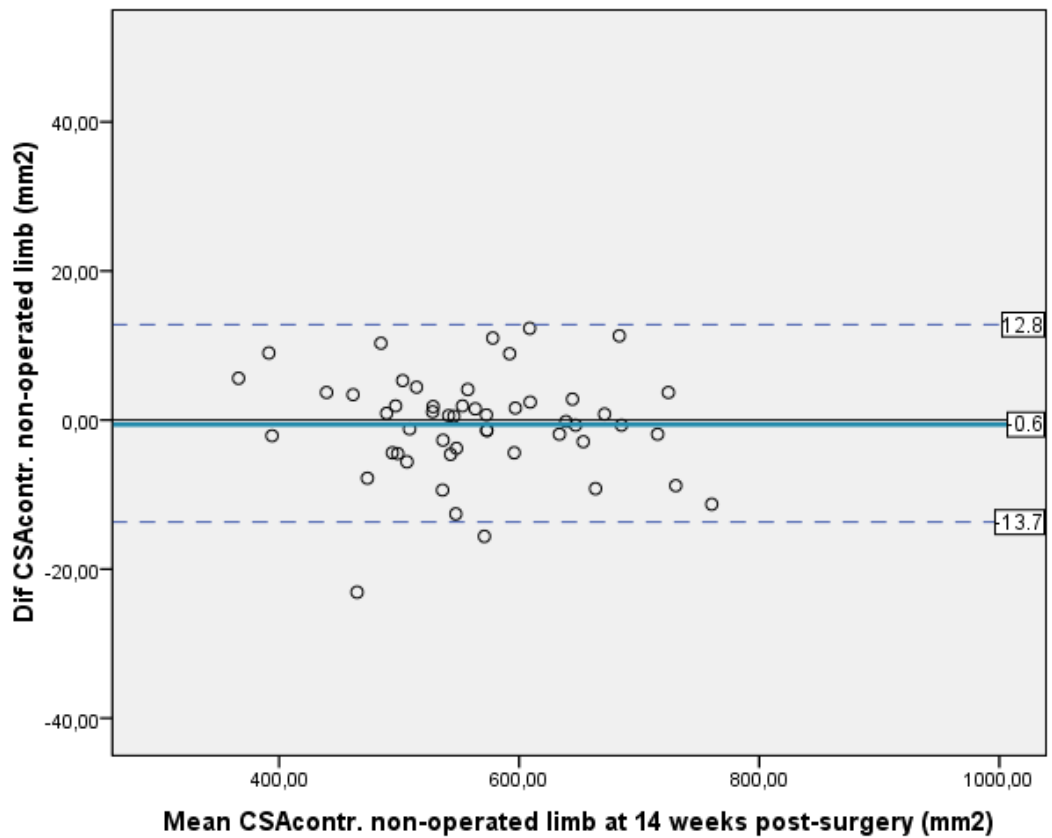
As shown in the Figure above (Figure 7.2d), for the non-operated limb, narrower LoA and greater levels of agreement were achieved compared to the operated limb, with a considerable number of patients' data points lying near zero.

Figure 7.2e Bland & Altman plot for rectus femoris CSA for the operated limb at 14 weeks post-TKR.



As shown from Figure 7.2e, narrow limits of agreement, and data points near zero, were observed. However, there is one outlier value away from the lower LoA, at 14 weeks post-TKR.

Figure 7.2f Bland & Altman plot for rectus femoris CSA for the non-operated limb at 14 weeks post-TKR.



Narrower LoA than the operated limb were observed at 14 weeks for the non-operated limb (Figure 7.2.f), and patients' data points relatively closely clustered around zero.

Appendix III: Participant Information sheet



Queen Margaret University
EDINBURGH



University Hospital of Patras

School of Health Sciences
Queen Margaret University Drive
Musselburgh
East Lothian
EH21 6UU

&

Orthopedic Medicine Department
Rio Patras
26504

PROJECT TITLE:

Effects of enhanced rehabilitation conditioning on the relationships between indices of sensori-motor, neuro-mechanical, psycho-physiological, and functional performance associated with patients following total knee replacement.

RESEARCHERS & COLLABORATORS:

María Moutzouri (Chief Investigator/PhD. Candidate)
Dr. John Giltsis (Consultant Orthopaedic Surgeon)
Prof. Elias Panagiotopoulos (Professor of Orthopaedics,
Director of Orthopaedic Clinic)

Dr Nigel Gleeson (Professor in Rehabilitation Science)
Dr. Fiona Couths (Senior Physiotherapist, Dean of the School of Health
Sciences)
Dr. Emad Al-dajali

PARTICIPANT INFORMATION SHEET

You are being invited to take part in the above titled research study. Before you decide to participate, it is important for you to understand why this research is being carried out and what it will involve. Please take your time to read the following information sheet and please feel free to ask any questions if there is anything that is not explained clearly. If you would like more information, please contact the research team (contact details are provided at the end of this information sheet).

WHAT IS THE PURPOSE OF THE STUDY?

This study is part of a doctoral research programme that is currently being undertaken at Queen Margaret University, Edinburgh. The research team are investigating whether we can enhance the rehabilitation that you will be receiving following your total knee replacement surgery.

This rehabilitative programme is detailed in the total knee replacement and rehabilitation patient advice booklet you have already received. If you have not yet received this, please contact the physiotherapy team. This information guide provides you with examples of the physiotherapy programme you are to receive. This will include strength, endurance, function, balance and other related techniques used within the field of physiotherapy. It is important that you follow the instructions given to you by the physiotherapy team as they will be important for your recovery following your surgery.

The primary aim of this study will be to investigate the effectiveness of standard practice integrated with new aspects of conditioning added that might potentially enhance the clinical care of patients. It will review the overall outcomes of surgery and rehabilitation while focusing on looking for any improved capability for you to produce strength, to move precisely, to self-perceive effort during exercise and to undertake activities from everyday life.

If you wish, after the research is complete, we can disseminate the findings from the study to you.

The findings may also be written and published in medical/scientific journals to aid other clinicians and patients elsewhere. Neither you nor your data will be identifiable in these publications.

WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

The only purpose of this study is to assess the best way to rehabilitate patients after total knee replacement surgery. The research team will keep your name, age, sex and your results in a record that will be stored on a password-protected computer to ensure only persons involved in the study can access the information. The storage and subsequent destruction of your data is compliant with the Data Protection Act 1998. All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves this hospital will have your name and address removed so that you cannot be identified from it, and will subsequently be anonymous.

COMPLAINTS

If you believe you have been harmed in any way by taking part in this study, you have the right to pursue a complaint. Details about this are available from the research team.

CONTACT DETAILS FOR FURTHER INFORMATION:

We hope you will participate in this study, but if you have any questions or would like more information, please contact:

Maria Moutzouri
Chief Investigator, Research Team.
Physiotherapist
Technological Educational Institute of Patras
(ATEI), Department of Physiotherapy
Aligon, 25100
TEL: 2691021150
MOBILE: 6977073125

E-mails: mmoutzouri@qmu.ac.uk
moutzouri_marie@yahoo.com (preferred correspondence)

WHO HAS REVIEWED THE STUDY?

For you to have been offered participation in this study, it will have had to have been already given a favourable ethical opinion for conduct in by Queen Margaret University Edinburgh's local Ethics Committee. It will also have been approved for scientific merit by the Local Research Scientific & Ethics Committee of University Hospital in Patras.

If you would like some independent advice about whether you should take part in the study, please contact:

Dr Billis Vicky
Physiotherapist- Associate Lecturer of
Physiotherapy
Technological Educational Institute (ATEI)
of Patras
Department of Physiotherapy
Tel 2691061150
Email: billis@tellam.gr

Prof. Tom Mercer
Professor of Exercise Physiology and
Rehabilitation (Physiotherapy)
School of Health Sciences
Queen Margaret University, Edinburgh
Queen Margaret University Drive
Musselburgh, East Lothian

WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?

The research findings may inform the research team that one way of rehabilitating patients is better than another. This will then alter the way the physiotherapy team suggest patients rehabilitate in the future.

Appendix IV: Informed Consent Form



Queen Margaret University
EDINBURGH



University Hospital of Patras
Orthopedic Medicine Department
Rio Patras
26504

&

School of Health Sciences
Queen Margaret University Drive
Musselburgh
East Lothian
EH21 6UU

PROJECT TITLE:

Effects of enhanced rehabilitation conditioning on the relationships between indices of sensori-motor, neuro-mechanical, psycho-physiological, and functional performance associated with patients following total knee replacement.

RESEARCHERS & COLLABORATORS:

Moutzouri Maria (Chief Investigator/PhD. Candidate)
Mr. Gilatis John (Consultant Orthopaedic Surgeon)
Prof. Panagiotopoulos Elias (Professor of Orthopaedics,
Director of Orthopaedic Clinic)

Prof. Nigel Gleeson (Reader in Rehabilitation Science)
Dr. Fiona Couthe (Senior Physiotherapist, Dean of the School of Health
Sciences)
Dr. Emad Al-djail

CONSENT FORM

Please initial box

1. I confirm that I have read and understand the information sheet provided for the above study.
I have had the opportunity to consider the information, ask any questions, and have had these answered satisfactorily.
2. I understand that my participation in this study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that data collected during this study may be looked at by responsible individuals from the University Hospital of Patras and Queen Margaret University throughout the course of this study.
4. I agree that the research team/physiotherapists may contact me by email, letter or telephone to discuss my rehabilitation progress should this be needed.
5. I agree to my GP being informed of my participation in the study.
6. I agree to take part in the above study.

Name of Participant

Date

Signature

Name of Researcher

Date

Signature

If you would like some independent advice about whether you should take part in the study, please contact:

Queen Margaret University, Edinburgh
Queen Margaret University Drive
Musselburgh
EH21 6UU
E-mail: tmercet@qmu.ac.uk

Appendix V: NHS & QMU Ethics Committee Approval



ΕΘΝΙΚΟ ΣΥΣΤΗΜΑ ΥΓΕΙΑΣ
Πανεπιστημιακό Γενικό Νοσοκομείο Πατρών
'ΠΑΝΑΓΙΑ Η ΒΟΗΘΕΙΑ'
26504 ΡΙΟ ΠΑΤΡΩΝ

NATIONAL HEALTH SYSTEM
GENERAL UNIVERSITY HOSPITAL OF PATRAS
26504 RION, PATRAS
GREECE

ΑΠΟΣΠΑΣΜΑ ΠΡΑΚΤΙΚΟΥ
ΤΗΣ ΑΡ16.23/8/11ΤΑΚΤΙΚΗΣ ΣΥΝΕΔΡΙΑΣΗΣ
ΤΗΣ ΕΠΙΤΡΟΠΗΣ ΗΘΙΚΗΣ, ΕΡΕΥΝΑΣ & ΔΕΟΝΤΟΛΟΓΙΑΣ
ΤΟΥ Π.Γ.Ν.Π.

REGULAR ASSESSMENT BOARD
OF RESEARCH ETHICS COMMITTEE OF U.G.H.P.
APPLICATION NUMBER 16.23/8/11

Today, Tuesday, on the 23rd of August 2011 at 9:30am, in the city of Patras the Research Ethics Committee (which has been constituted under law number 8/20.04.2010) of General University Hospital of Patras came into session in the Boarding room to assess and decide on the outcome of submitted research proposals. The President's invitation included regular and external members, and the following participated in the Assessment Board:

- | | |
|-----------------------------|----------------|
| 1. Tsolakis Ioannis | President |
| 2. Giannakenas Konstantinos | Regular Member |
| 3. Giannoulis Nickolaos | Regular Member |

Nikolaou Paraskeui was assigned as secretary of the session of the Committee.

Since all members were present, the Research Ethics Committee processed the topics defined by the President under decision number 16/22 8.2011.

Ο Πρόεδρος
Επιτροπής Έρευνας, Ηθικής
& Δεοντολογίας



Ιωάννης Τσολάκης
Καθηγητής Αγγειοχειρουργικής

1st Topic of Assessment board

The application (under protocol number 7052/ 4 - 7 -2011) of Miss Maria Moutzouri (PhD student of Queen Margaret University) Physiotherapist, Lecturer at ATEI of Patras for approval of her research project with title:

Effects of enhanced rehabilitation conditioning on the relationships between indices of sensori-motor, neuro-mechanical, psycho-physiological, and functional performance associated with patients following total knee replacement.

The current research project is a study for the fulfillment of PhD degree in Queen Margaret University, Edinburgh, UK, supervised by Professor Gleeson Nigel. The study will take place in General University Hospital of Patras with the support of Dr Gliatis J, Consultant Orthopedic Surgeon, Assistant Lecturer of Orthopedic Medicine and Dr Panagiotopoloulos E, Director of the Orthopedic Clinic.

The Research Ethics Committee upon discussion and taking under consideration all relevant documentation submitted by Miss Maria Moutzouri

DECIDED UNANIMOUSLY

And approved the participation of patients discharged from the Orthopedic Department of University Hospital of Patras to the research project for the fulfillment of the PhD Degree.

The President of
Research Ethics Committee
Ioannis Tsolakis
Professor of Angiosurgery

I verify the accuracy of the translation of the attached in Greek language certified original document in the English language, which is issued under law and according to the conditions of the "Lawyer's Codes".

Athens, 8.9.2011
The assenter lawyer

DEMETRIOS G. SKARIPAS
LAWYER
ΚΑΛΟΓΕΡΙΑΣ 10, ΑΘΗΝΑ
ΣΕΚΕΣ
Τηλ: 0030210369114
Tsolakis



ΑΝΑΡΤΗΣΙΜΟ Ε. Σ. ΣΚΑΡΙΠΑΣ
ΔΕΛΤΑ ΤΥΠΟΓΡΑΦΕΙΑΣ Α.Ε. (Π. Ο. ΜΑΥΡΟΣ)
ΑΡΧΑΙΑ ΟΔΟΣ ΤΡΙΠΛΗΣ 10, ΑΘΗΝΑ



Queen Margaret University
EDINBURGH

Maria Moutzouri
PhD student
Physiotherapy
Queen Margaret University

Sheila Adamson
Collaborations Development Co-ordinator
Queen Margaret University, Edinburgh
Queen Margaret University Drive
Musselburgh
East Lothian EH21 6UU

Direct Dial
Tel (0)131 474 0000 Fax (0)131 474 0001
Email: sadamson@qmu.ac.uk

22 May 2012

Dear Maria

Ethical Approval – Effects of enhanced rehabilitation conditioning on the relationships between indices of sensori-motor, neuro-mechanical, psycho-physiological, and functional performance associated with patients following total knee replacement.

Thank you for submitting documentation in relation to your application for ethical approval for the above project. Your application was considered by the Divisional Ethics Committee.

Lynne Flynn, Head of Division, has reviewed your application and has noted that the project has approval from the Scientific & Research Ethics Committee of the University Hospital, Rion in Patras where data collection will take place. She has confirmed that she is happy to grant full ethical approval for your research.

A standard condition of this ethical approval is that you are required to notify the University, in advance, of any significant proposed deviation from the original protocol. Reports are also required once the research is underway if there are any unexpected results or events that raise questions about the safety of the research. Please find the appropriate form for this on our website - <http://www.qmu.ac.uk/quality/rs/default.htm#ethics>

We would like to thank you for your co-operation and wish you well with your project.

Yours sincerely,

Sheila Adamson
Secretary to the Research Ethics Panel

Appendix VI: KOOS Questionnaire Form

Knee Injury and Osteoarthritis Outcome Score(KOOS)

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to do your usual activities.

Answer every question by ticking the appropriate box. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms - These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?	<input type="radio"/> Never	<input type="radio"/> Rarely	<input type="radio"/> Sometimes	<input type="radio"/> Often	<input type="radio"/> Always
S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?	<input type="radio"/> Never	<input type="radio"/> Rarely	<input type="radio"/> Sometimes	<input type="radio"/> Often	<input type="radio"/> Always
S3. Does your knee catch or hang up when moving?	<input type="radio"/> Never	<input type="radio"/> Rarely	<input type="radio"/> Sometimes	<input type="radio"/> Often	<input type="radio"/> Always
S4. Can you straighten your knee fully?	<input type="radio"/> Always	<input type="radio"/> Often	<input type="radio"/> Sometimes	<input type="radio"/> Rarely	<input type="radio"/> Never
S5. Can you bend your knee fully ?	<input type="radio"/> Always	<input type="radio"/> Often	<input type="radio"/> Sometimes	<input type="radio"/> Rarely	<input type="radio"/> Never

Stiffness - The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?	<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme
S7. How severe is your knee stiffness after sitting, lying or resting later in the day ?	<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme

Subtotal:

Pain

P1. How often do you experience knee pain?	<input type="radio"/> Never	<input type="radio"/> Monthly	<input type="radio"/> Weekly	<input type="radio"/> Daily	<input type="radio"/> Always
--	-----------------------------	-------------------------------	------------------------------	-----------------------------	------------------------------

What amount of knee pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your knee					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
P3. Straightening knee fully					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
P4. Bending knee fully					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
P5. Walking on flat surface					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
P6. Going up or down stairs					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
P7. At night while in bed					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
P8. Sitting or lying					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
P9. Standing upright					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	

Subtotal:

Function, daily living - The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	

A2. Ascending stairs					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A3. Rising from sitting					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	

A4. Standing					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	

A5. Bending to floor/pick up an object					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
A6. Walking on flat surface					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
A7. Getting in/out of car					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
A8. Going shopping					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
A9. Putting on socks/stockings					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
A10. Rising from bed					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
A11. Taking off socks/stockings					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
A12. Lying in bed (turning over, maintaining knee position)					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
A13. Getting in/out of bath					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
A14. Sitting					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
A15. Getting on/off toilet					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	
A17. Light domestic duties (cooking, dusting, etc)					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	

Subtotal

Function, sports and recreational activities - The following questions concern your

physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	

SP2. Running					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	

SP3. Jumping					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	

SP4. Twisting/pivoting on your injured knee					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	

SP5. Kneeling					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Extreme	

Subtotal:

Quality of Life

Q1. How often are you aware of your knee problem?					
<input type="radio"/> Never	<input type="radio"/> Monthly	<input type="radio"/> Weekly	<input type="radio"/> Daily	<input type="radio"/> Constantly	

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?					
<input type="radio"/> Not at all	<input type="radio"/> Mildly	<input type="radio"/> Moderately	<input type="radio"/> Severely	<input type="radio"/> Totally	

Q3. How much are you troubled with lack of confidence in your knee?					
<input type="radio"/> Not at all	<input type="radio"/> Mildly	<input type="radio"/> Moderately	<input type="radio"/> Severely	<input type="radio"/> Extremely	

Q4. In general, how much difficulty do you have with your knee?					
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderately	<input type="radio"/> Severe	<input type="radio"/> Extreme	

Subtotal:

Thank you very much for completing all the questions in this questionnaire.

Reference for Score: Roos, E.M. Roos, H.P. Lohmander, L.S. Ekdahl, C. Beynnon, B.D. (1998) Knee Injury and Osteoarthritis Outcome Score (KOOS) - Development of a self-administered outcome measure. *J Orthop Sports Phys Ther.* 28(2), 88-96.

Appendix VII: KOS-ADL Questionnaire Form
Knee Outcome Survey Activities of Daily Living
Scale (ADLS).

Symptoms: To what degree does each of the following symptoms affect your level of activity? (check one answer on each line)

	I do not have the symptom	I have the symptom, but it does not affect my activity	The symptom affects my activity slightly	The symptom affects my activity moderately	The symptom affects my activity severely	The symptom prevents me from all daily activity
Pain	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Stiffness	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Swelling	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Giving way, buckling, or shifting of the knee	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Weakness	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Limping	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Functional Limitations With Activities of Daily Living: How does your knee affect your ability to: (check one answer on each line)

	Activity is not difficult	Activity is minimally difficult	Activity is somewhat difficult	Activity is fairly difficult	Activity is very difficult	I am unable to do the activity
<u>Walk</u>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Go up stairs	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Go down stairs	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Stand	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Kneel on front of your knee	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Squat	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Sit with your knee bent	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Rise from a chair	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Scoring: The first column is scored 5 points for each item, followed in successive columns by scores of 4, 3, 2, 1, and 0

Appendix VIII: SF-12 Questionnaire Form.

SF-12® Patient Questionnaire

Page 1 of 3

Patient Initials _____ Date of Birth: ___/___/___ Patkey: _____
Surgeon Name: _____ Date: _____
Examination Period: _____ Preop (1) _____ 3 Year (4)
_____ Immediate Postop (2) _____ 5 Year (5)
_____ 1 Year (3) _____ Other (specify) (6): _____

SF-12®:

This information will help your doctors keep track of how you feel and how well you are able to do your usual activities. Answer every question by placing a check mark on the line in front of the appropriate answer. It is not specific for arthritis. If you are unsure about how to answer a question, please give the best answer you can and make a written comment beside your answer.

1. In general, would you say your health is:

- _____ Excellent (1)
- _____ Very Good (2)
- _____ Good (3)
- _____ Fair (4)
- _____ Poor (5)

The following two questions are about activities you might do during a typical day. Does YOUR HEALTH NOW LIMIT YOU in these activities? If so, how much?

2. MODERATE ACTIVITIES, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf:

- _____ Yes, Limited A Lot (1)
- _____ Yes, Limited A Little (2)
- _____ No, Not Limited At All (3)

3. Climbing SEVERAL flights of stairs:

- _____ Yes, Limited A Lot (1)
- _____ Yes, Limited A Little (2)
- _____ No, Not Limited At All (3)

During the PAST 4 WEEKS have you had any of the following problems with your work or other regular activities AS A RESULT OF YOUR PHYSICAL HEALTH?

4. ACCOMPLISHED LESS than you would like:

- _____ Yes (1)
- _____ No (2)

5. Were limited in the KIND of work or other activities:

- _____ Yes (1)
- _____ No (2)

Surgeon Initials _____ Date: _____

Patient Initials: _____ Date of Birth: ____/____/____ Patkey: _____

Surgeon Name: _____ Date: _____

Examination Period: _____ Preop (1) _____ 3 Year (4)
 _____ Immediate Postop (2) _____ 5 Year (5)
 _____ 1 Year (3) _____ Other (specify) (6): _____

SF-12® Cont'd:

During the PAST 4 WEEKS, were you limited in the kind of work you do or other regular activities AS A RESULT OF ANY EMOTIONAL PROBLEMS (such as feeling depressed or anxious)?

6. ACCOMPLISHED LESS than you would like:

- _____ Yes (1)
 _____ No (2)

7. Didn't do work or other activities as CAREFULLY as usual:

- _____ Yes (1)
 _____ No (2)

8. During the PAST 4 WEEKS, how much did PAIN interfere with your normal work (including both work outside the home and housework)?

- _____ Not At All (1)
 _____ A Little Bit (2)
 _____ Moderately (3)
 _____ Quite A Bit (4)
 _____ Extremely (5)

The next three questions are about how you feel and how things have been DURING THE PAST 4 WEEKS. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the PAST 4 WEEKS –

9. Have you felt calm and peaceful?

- _____ All of the Time (1)
 _____ Most of the Time (2)
 _____ A Good Bit of the Time (3)
 _____ Some of the Time (4)
 _____ A Little of the Time (5)
 _____ None of the Time (6)

Surgeon Initials _____ Date: _____

Patient Initials _____ Date of Birth: ____/____/____

Patkey: _____

Surgeon Name: _____

Date: _____

Examination Period: _____ Preop (1) _____ 3 Year (4)
 _____ Immediate Postop (2) _____ 5 Year (5)
 _____ 1 Year (3) _____ Other (specify) (6): _____

SF-12® Cont'd:

10. Did you have a lot of energy?

- _____ All of the Time (1)
 _____ Most of the Time (2)
 _____ A Good Bit of the Time (3)
 _____ Some of the Time (4)
 _____ A Little of the Time (5)
 _____ None of the Time (6)

11. Have you felt downhearted and blue?

- _____ All of the Time (1)
 _____ Most of the Time (2)
 _____ A Good Bit of the Time (3)
 _____ Some of the Time (4)
 _____ A Little of the Time (5)
 _____ None of the Time (6)

12. During the PAST 4 WEEKS, how much of the time has your PHYSICAL HEALTH OR EMOTIONAL PROBLEMS interfered with your social activities (like visiting with friends, relatives, etc.)?

- _____ All of the Time (1)
 _____ Most of the Time (2)
 _____ A Good Bit of the Time (3)
 _____ Some of the Time (4)
 _____ A Little of the Time (5)
 _____ None of the Time (6)

Surgeon Signature _____ Date _____

Appendix IX: CONSORT Checklist.

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Appendix X: Published papers from thesis within the Literature



Systematic review

What is the effect of sensori-motor training on functional outcome and balance performance of patients' undergoing TKR? A systematic review

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Abstract

Objectives Total knee replacement (TKR) has a beneficial effect on patients' functional ability; however, incidence of falls and deficits on proprioception are not restored even 1-year after surgery. Early and intensive exercise post-TKR has received limited endorsement in the literature. The aim of this review was to systemically identify and critically appraise clinical studies investigating the effect of sensori-motor training on functional and balance performance in TKR patients.

Data sources The electronic databases Cochrane Library, MEDLINE, EMBASE, CINAHL, PEDro and the register of current controlled trials were searched up to September 2014.

Review methods Two independent reviewers used predefined inclusion and exclusion criteria to identify all eligible articles. Eligible articles were summarized and critically reviewed, using the PEDro scale.

Results Two hundred and seventy six articles were screened, six were included. The studies, presented the results of 409 patients (269 intervention, 140 control). A range of rehabilitation protocols were defined by components of proprioception, postural control, balance perturbation and coordination. All studies supported the use of sensori-motor training as an additional element in patients' rehabilitation protocols. Clinical performance-based tests (more than relevant patient-reported measures) showed that functional ability and balance were improved compared to controls. The robustness of evidence was compromised because most of the studies were underpowered.

Conclusions Limited robust (1a) evidence supports the equal effectiveness of functional rehabilitation program as a functional rehabilitation enhanced with sensori-motor elements in patients post-TKR. However, dose-response parameters of exercise eliciting improvement warrant further investigation.

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Keywords: Balance control; Balance training; Sensori-motor training; Proprioception training; Knee replacement; Systematic review

Introduction

Approximately 60 to 80% of patients with osteoarthritis (OA) of the knee report knee instability, which affects sensori-motor and postural control, incidence of falls and

ability to perform every-day life (ADL) activities [1–4]. Evidence from studies investigating the effect of total knee replacement (TKR), as a treatment to knee OA, showed gradual restoration of sensori-motor and functional abilities without however, reaching full recovery, even at 6-months postsurgery [5–11]. There is a 27% postsurgery reduction in patient' numbers exceeding cut-off criteria for falls-risk in the elderly (14 seconds, TUG test), indicating that falls-likelihood and restrictions to quality of life (QOL), is reduced but not eliminated [9–11].

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Studies investigating traditional 'cornerstones' of TKR recovery involving exercise programs with ROM and strengthening exercises, have shown small beneficial effects. Functional rehabilitation (exercises mimicking ADL mostly in weight-bearing positions) has shown better results, but the improvement has presented a plateau at 3 to 6 months [12,13]. Importantly, proprioception training demonstrated efficacy for balance performance in patients with OA of the knee [14,15]. Sensori-motor training has been found to improve proprioception, strength, and postural stability in lower extremity rehabilitation [3,15,16,20]. Balance and proprioception training has been characterized as sensori-motor training, first developed by Dr. Vladimír Janda, as part of a treatment approach to chronic musculoskeletal pain syndromes. Their role in rehabilitation is to challenge the sensori-motor system and restore normal motor programs. A recent systematic review investigating the effect of physical exercise after TKR included some of the studies with sensori-motor training [17]. The review showed that sensori-motor training could serve as a novel clinically appropriate rehabilitation refinement to traditional approaches in TKR patients [17]. Nevertheless, its dose-response characteristics, frequency and intensity/numbers of exercises have not been clarified.

A special form of therapeutic exercise designed to address, not only isolated strengthening of a group of muscles, but also enhances central nervous system (CNS). For example, function of the CNS in regulating movement in order to reach proper firing patterns for maintaining joint stability is characterized as sensori-motor training [18,19]. Sensori-motor training is thought to stimulate afferent information of joint sensors and therefore influence muscle activity and neuromuscular control scheme [18]. It is often used for the management of patients with chronic musculoskeletal pain syndromes and sports injuries [3,20,21]. Components of balance and proprioception usually include closed kinetic chain exercise aiming to challenge balance and knee stability such as retro-walking, side-walking, overcoming obstacles, exercise on wobble boards and generally weight-bearing tasks [3,21].

From the analysis of the available literature, it was evident that important questions, such as components of sensori-motor training added to the usual functional physiotherapy regime, timing of initiation, intensity/numbers of exercises and parameters influencing effectiveness, remained unanswered. The aim of the current systematic review was to analyze all published randomized controlled trials (RCTs) that have included sensori-motor components in TKR patients' physiotherapy rehabilitation program in order to assess the effect on physical function, performance tasks, pain relief and balance status. Moreover, potential answers in the aforementioned questions, such as the timing of when to best initiate such a program during the rehabilitation period, as well as the optimal frequency/number of balance exercises to be added to usual physiotherapy programs, was evaluated.

Methods

Search strategy

The electronic databases: the Cochrane Central Register of Controlled Trials (Cochrane Library), MEDLINE, EMBASE (via ProQuest), Biomed Central, Cinahl (via EBSCO host) and Physiotherapy Evidence Database (PEDro) were searched from 1995 to December 2014. The MEDLINE Mesh search strategy adopted for the study is displayed in Appendix I. Randomized controlled trials were only included if published in the English language. The reference lists of all eligible papers were also screened to identify any missing studies.

Eligibility criteria

Eligibility assessment was performed independently in a standardized manner and disagreements amongst reviewers were resolved by consensus. Therefore studies were included if they fulfilled the following five criteria:

1. Participants underwent primary TKR.
2. An exercise-based intervention incorporating sensori-motor components was involved compared or not with another therapeutic intervention, placebo or control.
3. Balance and/or functional performance was/were used as outcome measure/s.
4. Study design was a randomized design [22]
5. The full paper was published in the English language.

All cadaver or animal studies were excluded. Moreover, studies with samples involving patients with rheumatoid arthritis (RA) were excluded.

Study identification

Two evaluators independently selected the studies based on titles and abstracts, excluding those not related to the subject. The full text was obtained for all papers that were considered potentially relevant. Once collected, these were reviewed by both reviewers to determine if eligibility criteria were fulfilled. The studies finally included were analyzed according to a certain structure: author/year, sample, study design, assessment outcome measures, timeline, physiotherapy treatment, equipment and effects. Each reviewer assessed the methodological quality of the included studies independently using the PEDro criteria [23].

Critical appraisal

Studies were analyzed for methodological quality using the PEDro ten point scale [23] which assesses internal validity and interpretation of each trial.

Please cite this article in press as: Moutzouri M, et al. What is the effect of sensori-motor training on functional outcome and balance performance of patients' undergoing TKR? A systematic review. *Physiotherapy* (2015), <http://dx.doi.org/10.1016/j.physio.2015.11.001>

Data analysis

In the first stage, the analysis involved a critical appraisal process of the studies according to the PEDro scale determining the methodological quality of the included studies (Table 1).

In the next stage, a descriptive review of studies incorporating a physiotherapy program with components of sensori-motor training in patients after TKR, was undertaken (Table 2).

All data extracted from the studies were analyzed independently by two reviewers (MM and RP) and were subsequently discussed. Disagreements were resolved by a third reviewer (NG).

Results

A total of 276 citations were identified from the search strategy, summarized in Fig. 1. In the initial search, 237 studies were excluded because the title, abstract or keywords did not match the proposed theme. Of the 39 that remained, nine were excluded due to the non-English language used, sample comorbidities such as RA and cadaver samples. Twenty studies were excluded as they had assessed balance and falls following a conventional physiotherapy program, but without incorporating sensori-motor training. Therefore six studies (five randomized controlled trials – RCTs – and one cohort study) were deemed eligible and were finally included in the review [23–30]. The results of the critical appraisal according to PEDro scale are presented in Table 1.

The quality of the studies was assessed in a first stage as although all studies satisfied a similar number of criteria for inclusion, their methodologies varied substantially.

Critical appraisal of studies' methodological quality

Table 2 presents critical appraisal of all studies (PEDro), except for the non-RCT study by Gauchard *et al.* [30]. All studies offered adequate robustness in methodology (PEDro: 5 to 7) with clearly defined research questions, population' characteristics and methods of assessing balance.

All included studies provided clear sampling descriptions (numbers, age, gender and pathology), acceptable recruitment methods and drop-out rates. A consistent limitation was that all, except for one study [29], had used experimental design sensitivity criteria to compute sample size' requirements. The studies by Liao *et al.* [28] and Gstoettner *et al.* [26] provided statistically significant improvement between groups in some of the outcome measures tested, without however, reporting effect sizes. The study by Piva *et al.* [27] was labeled as 'pilot', but lacked a significant treatment effect or had been underpowered. Similarly, the study by Fung *et al.* [25] offered high rates of retention of null-hypotheses (inflated type-II error).

Participants

Patients had primary OA (grade III–IV, Kellgren and Lawrence system) and fulfilled criteria to undergo TKR (same prosthesis; cemented; cruciate retention). The six studies included 409 subjects (269 randomized allocated to intervention; 140 to control group).

Outcome measures

All studies used validated measures [24] to assess balance despite the absence of 'gold standard' criteria. Parameters used were static or dynamic balance during either single or double leg stance, or during a functional task. Patient-reported outcomes including Activity-specific Balance Confidence Scale (ABCS) were used [25]. Sophisticated equipment (force plates; balance-platforms [Biodex stability system]) measuring postural sway, center of mass (COM) transference, bilateral dynamic stance [26], or center of pressure (COP), assessments of gait speed and function [WOMAC, Knee Society Score (KSS), Lower Extremity Functional Scale (LEFS), SF-36] [25–29], clinical functional outcomes Timed Up and Go test (TUG), functional reach test, single leg standing balance (SLSB), stair climb test [27,28], and dual platform posturography [30], were used.

Sensori-motor interventions

Piva *et al.* and Liao *et al.* [27,28], implemented conceptually similar protocols of functional exercise training, which had previously been tested for their effectiveness [16] in enhancing sensori-motor training [4,31,32]. Protocols involved 6- and 8-weeks' supervised programs. However, Liao *et al.*'s study [28] also entailed a subsequent 4-month home program. These two studies [27,28] as well as the study of Gstoettner *et al.* [26] focused on balance exercise training involving agility and perturbation techniques (side walking, cross-over steps, single leg standing). Other studies have used relevant balance exercise in an aquatic environment using float cuffs [29] or Nintendo Wii-fit game platform-based exercises to engage lateral weight shifting, multidirectional balance and static/dynamic postural control [24], using full weight-bearing functional and proprioception exercises, mimicking ADL [26–28,30].

Timing of initiation

Some studies have started implementing the sensori-motor training at least 2-months postoperatively, in order to ensure pain and effusion elimination [29,31,32], others incorporated sensori-motor elements within days of surgery using land or aquatics programs [33,34] or even, preoperatively [30]. Notably, all pre and postsurgery TKR interventions were tolerated well by patients, with no adverse effects reported.

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Table 1
Description of studies including Sensori-motor training in TKR patients.

Study	Sample	Age	Intervention	Dose	Intensity progression	Setting	Start of program	End of program	Main outcome measures	Final follow-up	Results	Treatment effect
Peng et al. 2012 [25]	IG n=27 (19F); CG n=23 (14F)	68	IG: Strengthening exercise + WB-FR balance challenging; CG: Strengthening posture-balance exercise	60 minutes + 15 minutes WB FR frequency/duration (weeks) NS	Exercise progressed	Outpatient clinic-supervised	Average 37 days after surgery	Average 54 days after surgery	Active ROM: 2MWT, NPBS; LEPS; ABCS; LEK	Average 54 days after surgery	Significant difference only for LEPS between groups favoring IG	Medium DS for LEPS
Gauchard et al. 2010 [30]	IG n=20 (16F); TKR1 CG: 68	IG: 70; CG: 68	IG: Passive/active mobilization, quadriceps exercise + proprioceptive gait and functional exercise; CG: no PT	34 to 41 days frequency/dose NS	NS	Inpatient clinic-supervised	1st post-op day	34 to 41 days	Static and dynamic posturography, SGR	34 to 41 days	TKR1: IG statistically significant lower static balance performance at 17-26days compared to CG; Static/dynamic, not static balance; IG TKR2 to CG, at 34 to 41 days	NS
Osborne et al. 2010 [35]	IG n=18 (16F); CG n=20 (14F)	IG: 73; CG: 67	IG: Proprioceptive training and walking, stretching; CG: NS	Daily for 45 minutes (15 minutes standard + 30 minutes proprioceptive)	Exercise progressed	Home-based program; supervised once a week at clinic	6 weeks pre-op	At time of TKR	Balance (Bilateral stance), Chair Stand Test, Timed Stair test, WOMAC, KSS	6 weeks after surgery	Stat significant difference in balance in IG, no difference in CG. Stat significant difference between groups favoring IG	Small
Liao et al. 2013 [28]	IG n=38 (40F); CG n=35 (37F)	IG: 73; CG: 71	IG: Functional + balance training; CG: Functional training	90 minutes (30 minutes functional + 60 minutes balance; frequency NS)	Exercise progressed	Outpatient clinic-supervised	At least 2 months after surgery	8 weeks	FRY, SLST, 10MWT, TUG, 30 SCR, WOMAC	8 weeks after start program	IG more significant effects on physical performance and WOMAC than CG	IG better 29% SLST; 18% gait speed; 13% WOMAC; 31% FRY; 9% TUG than CG
Licht et al. 2012 [29]	IG n=66; CG n=69	IG: 68.5; CG: 70.9	IG: early aquatic therapy; CG: late aquatic ther. Aquatic (proprioception, coordination, strengthening) + PT program	3-week for 30 minutes balance + daily PT	NS	Clinic-based supervised	IG: 6th Post-op day; CG: 14th Post-op day	Up to 5 weeks	WOMAC; SF-36	24 months	Mean outcomes better in the IG. Not statistically significant. Clinical significant WOMAC 24m= 6.3 units (with a MDC3= 3.3)	WOMAC
Pru et al. 2010 [27]	IG n=18 (13F); CG n=17 (12F)	IG: 70; CG: 67	IG: Functional + balance training; CG: Functional training	12 sessions of 90 minutes (30 minutes functional, 60 minutes balance) + home based program for 4months (2/week)	Exercise progressed	Clinic-based supervised	2 to 4 months after surgery	6 weeks after start program	Gait speed; SLST, 10MWT, TUG, 30SCR, WOMAC, LEPS	6 months	Clinically significant effects in gait speed, SLST, WOMAC stiffness and pain favoring IG	IG: 16% gait speed, 24% SLST

CG, control group; IG, intervention group; TKR, total knee replacement; NS, not stated.

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Table 2
Description of studies including Sensori-motor training in TKR patients.

Study	Sample	Age	Intervention	Dose	Intensity progression	Setting	Start of program	End of program	Main outcome measures	Final follow-up	Results	Treatment effect
Fung et al. 2012 [25]	IG n = 27 (19F); CG n = 23 (14F)	68	I	60 minutes + 15 minutes Wii fit. frequency/duration (weeks) NS	Exercise progressed	Outpatient clinic-supervised	Average 37 days after surgery	Average 54 days after surgery	Active ROM; 2 MWT; NPRS; LEFS; ABCS; LGR	Average 54 days after surgery	Significant difference only for LEFS between groups favoring IG	Medium ES for LEFS
Gauchard et al. 2010 [30]	IG n = 20 (16F); TKR ₁ post-ography at 17 to 20 days post-op; TKR ₂ post-ography at 34 to 41 days post-op. CG n = 10 (8F) healthy	IG: 70; CG: 68	IG: Passive/active mobilization, quadriceps exercise + proprioceptive gait and functional exercise; CG: no PT	34 to 41 days frequency/dose NS	NS	Inpatient clinic-supervised	1st post-op day	34-41 days	Static and dynamic posturography, SOT	34 to 41 days	IG statistically significant lower static balance performance at 17 to 20 days compared to CG; Similar dynamic, not static balance IG TKR ₂ to CG, at 34 to 41 days.	NS
Grothner et al. 2010 [26]	IG n = 18 (16F); CG n = 20 (14F)	IG: 73; CG: 67	IG: Proprioceptive training and walking, stretching; CG: NS	Daily for 45 minutes (15 minutes standard + 30 minutes proprioceptive)	Exercise progressed	Home-based program; supervised once a week at clinic	6 weeks pre-op	At time of TKR	Balance (bilateral stance), Gait Speed Timed Stair test, WOMAC, KSS	6 weeks after surgery	Stat significant difference in balance in TG, no difference in CG. Stat significant difference between groups favoring TG	Small
Liao et al. 2013 [28]	IG n = 58 (46F); CG n = 55 (37F)	IG: 73; CG: 71	IG: Functional + balance training; CG: Functional training	90 minutes (30 minutes functional + 60 minutes balance; Frequency NS	Exercise progressed	Outpatient clinic-supervised	At least 2 months after surgery	8 weeks	FRT; SLST; 10MW; TUG, 30 SCR, WOMAC	8 weeks after start program	IG more significant effects on physical performance and WOMAC than CG	IG better 20% SLST; 18% gait speed; 13% WOMAC; 31% FRT; 9% TUG than CG
Liebs et al. 2012 [29]	IG n = 66; CG n = 69	IG: 68.5; CG: 70.9	IG: early aquatic therapy; CG: late aquatic ther. Aquatic (proprioception, coordination, strengthening) + PT program	3/week for 30 minutes balance + daily PT	NS	Clinic-based supervised	IG: 6th Post-op day; CG: 14th post-op day	Up to 5 weeks	WOMAC, SF-36	24 months	Mean outcomes better in the TG. Not statistically significant. Clinical significant WOMAC 24-6.9 units (with a MICD = 5.3)	ES = 0.2 to 0.3 in WOMAC
Piva et al. 2010 [27]	IG n = 18 (13F); CG n = 17 (12F)	IG: 70; CG: 67	IG: Functional + balance training; CG: Functional training	12 sessions of 90 minutes (30 minutes functional, 60 minutes balance) + home based program for 4 months (2/week)	Exercise progressed	Clinic-based supervised	2 to 4 months after surgery	6 weeks after start program	Gait speed; SLST, 10 MWT; TUG, 30 S CRT, WOMAC, LEFS	6 months	Clinically significant effects in gait speed, SLST, WOMAC stiffness and pain favoring IG	IG: 8% gait speed, 24% SLST

CG, control group; IG, intervention group; TKR, total knee replacement; NS, not stated.

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Volume–duration of exercise

In the previously described studies by Piva *et al.* [27] and Liao *et al.* [28] that had shared a common format of delivery, the volume of exercise implemented in control and intervention groups was not equal, with the intervention group receiving 30 minutes more training in each session. By contrast, the study by Fung *et al.* [25] was iso-volumetric across groups but did not report the frequency of sessions undertaken by each group. Non iso-volumetric conditioning was noted in the study by Gstoettner *et al.* [27], in which the intervention group's training consisted of a 6-week, 6-session prehabilitation program (45 minutes session duration), which had not been matched with the program of the control group. Similarly, the study by Liebs *et al.* [29] reported earlier initiation (by several days) of post-TKR sensori-motor conditioning for the intervention group, compared to controls (6th vs 14th post-operative day). The time-line of each of the included studies, in terms of baseline measurement, intervention period and follow-up are presented in Fig. 2.

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Progression

Criteria for patients' progression (via re-assessment) were not detailed within the manuscripts. Progression for patients in the study by Fung *et al.* [25], that implemented sensori-motor training with the Wii-Fit, had been regulated according to similar exercises already performed successfully in physiotherapy treatment [25], without experiencing increased pain, effusion, giving away and decreases in ROM [23], or by clinical review of their capabilities [22]. In several studies [28–30], no progression was reported throughout the rehabilitation period.

Follow-up

Most of the studies followed-up patients for 2 to 6 months after surgery [25–28,30], apart from the study by Liebs *et al.*

[29] that had followed-up patients for up to 2-years post-operatively.

Effects on pain and function

The study by Liebs *et al.* [29], showed that early compared to late initiation (6th vs 14th postoperative day) of aquatic sensori-motor training led to superior improvements in function and quality of life (mean scores in WOMAC at 2-year follow-up; and although these results were not statistically significant, they exceeded minimal clinical important criteria for WOMAC across publications. Liao *et al.* [28] showed statistically significant change in scores (between 36 and 50% in WOMAC and functional tests such as TUG, stair-climb test, functional reach test) for an 8-week program ($n = 113$) of the group with the additional balance exercises to functional training compared to functional training group alone. Over a shorter intervention (6-weeks), Piva *et al.* [26] in a study using the same intervention groups as the study by Liao *et al.* [28], yielded no statistical change in scores ($n = 43$). Similarly, Gstoettner *et al.* [26] showed no across group (proprioception training vs control group) differences on function (WOMAC and KSS) after prehabilitation but improvement across groups was shown after TKR. Fung *et al.* [25] showed equivalent improvement in pain and functional performance (Numeric Pain Rating Scale and LEFS) between the usual care group and the group with the additional Wii-Fit training 2-months after TKR.

Effects on balance

Augmentation with balance exercises elicited approximately 25% postsurgery improvements in SLSB compared to baseline [27,28], 15% gains in patients' balance confidence compared to controls [25], and statistically significant ($P = 0.045$) postsurgery gains in bipedal stance performance with prehabilitation compared to controls [26]. Posturographic testing in the study by Gauchard *et al.* [30] showed improvements ($P = 0.07$) similar to that of age-matched controls. In the open-eyes' condition of the dynamic tests, although improvement did not reach statistical significance ($P = 0.07$), it was clearly more than that of controls, at 6-weeks post-TKR [30].

Discussion

Functionally intensive rehabilitation programs have elicited enhanced physical performance outcomes post-TKR [12,13], but deficits in movement control and balance remain [7–15]. In order to address these deficits exercise programs that include activities that challenge knee stability may be more appropriate [20,21]. Functional rehabilitation augmented by targeted sensori-motor conditioning (i.e. weight-bearing exercises involving twisting, changing direction, sudden start-stops, negotiation of unstable surfaces and

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obstacle) could potentially address these deficits and offer improved physical activity, postural control and prevent falls. Improving postural control and lowering falls-related injuries will reduce health-care costs. However, there is no available information on the costs associated with sensori-motor program replication or the cost-effectiveness of exercise programs aimed at preventing falls in TKR patients. Results from this systematic review suggest that sensori-motor training induces equivalent improvement between intervention and control group [25,27], indicating that sensori-motor training is an acceptable adjunct to usual care in physiotherapy. The studies by Liao *et al.* [28] and Gstoettner *et al.* [26] favored sensori-motor training; both studies showed a greater effect of additional sensori-motor training on the usual care on these persisting deficits, bridging a potential gap in rehabilitation programs. Moreover, studies report sensori-motor conditioning interventions as a therapeutic means which is entertaining for patients [29], is independent of specialized equipment (e.g. Wii fit) and environment (e.g. land or water-based), has the capability of producing movements with less energy expenditure [6,32] and importantly, offers no adverse effects to patients in any study reviewed. Moreover, the inclusion of dynamic stabilization exercises and eyes-closed exercises was highlighted as important [30].

Exact mechanisms underpinning how TKR impacts on mechanoreceptors remains elusive. The reviewed studies suggested mild improvements in balance following TKR [26,28,30]. These kinds of additional sensori-motor interventions activate proprioceptors in the ankle and hip joint, as well as proprioceptors in muscular, tendon and ligament tissues (e.g. posterior cruciate ligament) at the knee, since articular proprioceptors have been resected during TKR. These improvements may also result from retensioned capsuloligament structures (e.g. collateral ligaments), reduced pain and inflammation in the knee joint following the surgery [29]. Moreover, gradual functional and sensori-motor training after TKR induces restoration to intra-sensory proprioceptive compensation either at knee or other joints (hip/ankle) [30]. Therefore, corrective compensatory strategies regulate better postural control through neuroplasticity, involving improved muscle activation synergies, movement patterns, joint torques and contact forces that are disturbed during OA degeneration [30,34]. As a result, sensori-motor training potentially influences central mechanisms and motor responses that promote physical function, and potentially sensory function and stability [34,35].

Observation studies have showed that muscle coordination and proprioception is deficient even 6-months after TKR [10,11,36]. Two-month postsurgery period was considered sufficient to avoid pain and effusion exacerbation for the safe initiation of sensori-motor training [25,27,28], and to have provoked no adverse effects. Therefore, given the clinically important results by the studies by Liebs, Piva and Liao [27–29], it can be understood that the initiation of sensori-motor training within the first 2-months postsurgery, is acceptable and essential. Thus, any compensatory

protective strategies in proprioceptive and gait control, already learned and established in patients with knee OA, that had been associated with the pathway leading to TKR [1,2,31], would be eliminated. However, studies that had initiated programs early (6th day post-TKR) vs late (14th day) offered marginal patient-reported gains (WOMAC, medium effect size [29,30]. Interestingly, total hip replacement patients showed that early vs late training can give opposite outcomes compared to TKR patients, suggesting surgery-specific mechanisms of recovery [29]. The study by Gauchard *et al.* [30] investigated recovery of posturo-motor strategies post-TKR at two stages: firstly, after the elimination of pain and secondly, after a 6-week enhanced sensori-motor rehabilitation program (started within a few days after TKR), also showed that postural regulation (posturography analysis) required approximately 1-month to reach that of age-matched controls. Thus, a safe time for clinicians to initiate sensori-motor training seems to be within 2 weeks from TKR.

Regarding duration of the sensori-motor rehabilitation, most of the studies reviewed had implemented 6 to 8 week programs of supervised exercise (>1 session/week; 45 to 90 minutes). Nevertheless, optimal frequency, time and progression of dosage remain elusive due to methodological heterogeneity. Intervention groups in all studies offered improved functional and balance outcomes compared to controls when functional rehabilitation had been augmented with sensori-motor conditioning. No study had reflected an iso-volumetric comparison (between usual care and usual care enhanced with sensori-motor elements), hindering evaluation of any possible advantages by sensori-motor conditioning. Dose–response effects may therefore have been implicated in any gains that had been observed.

It was notable that patient-reported outcome measures (e.g. LEFS, ABCS, WOMAC) could not always detect the changes identified by objective functional and balance measures, such as TUG test and SLSB, known for their good clinimetric responsiveness and prognostic validity of falls-likelihood [25,27].

Underpinning the points for discussion in this review, was evidence from RCTs (except one [30]), offering Level Ia robustness (PEDro scale 5 to 7), sound methodologies and minimal patient' numbers lost-to-follow-up.

Limitations

This review has identified six studies investigating the effects of sensori-motor training when these are added to the physiotherapy regime post-TKR surgery. PEDro scoring suggested adequate robustness of methodological approaches in the five studies that were scored. Nevertheless, the experimental design of most studies was underpowered and had shunned iso-volumetric comparisons, precluding robust interpretation of the contribution of balance and proprioception conditioning, and also the generalization of outcomes. Heterogeneity of outcome measures, timing of conditioning initiation, and intensity/frequency of exercise, precluded

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meta-analytical approaches for the synthesis of evidence. Therefore, this systematic review offered novel qualitative data on the effect of sensori-motor training and speculation on its optimal implementation. The inclusion of only English language studies might have introduced bias, while the exclusion of patients (from the sample) with co-morbidities such as rheumatoid arthritis, limited the generalization of findings. All studies in this review offered critical discussion of findings, description of potential clinical impact, and contextualization within contemporary literature. However, although the sample recruitment and selection was acceptable, generalization of findings should be made with caution, and was only feasible in patients with knee OA undergoing primary TKR.

Conclusion

The review's findings provide encouraging qualitative data on the incorporation of sensori-motor training into the usual functional physiotherapy programs. This approach offers an acceptable and targeted intervention in improving functional performance and balance in patients after TKR. Sensori-motor training implemented for 6 to 8 weeks and initiated two weeks post-TKR, may be effective and tolerated well by patients, with no fear of adverse effects in physical function. However, a lack of acceptable effect size in some studies, combined with underpowered experimental designs, suggested both the possibility of either a lack of potency of intervention or a compromised capability to detect subtle gains that might have been offered by the intervention. Both aspects threaten what might be generalized from the findings in this population. Optimal intensity/frequency of exercise and criteria of progression warrant further investigation.

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Conflict of interest: No conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.physio.2015.11.001>.

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Corrigendum

Corrigendum to “What is the effect of sensori-motor training on functional outcome and balance performance of patients’ undergoing TKR? A systematic review”
[Physiotherapy 102 (2016) 136–144]



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The authors regret that Table 2 did not appear correctly in their article. The correct table should appear as below. The authors would like to apologise for any inconvenience caused.

Table 2
PEDro scale score for RCTs including sensori-motor training in TKR patients.

PEDro scale	Fung et al. (2012)	Gsoettner et al. (2010)	Liao et al. (2013)	Liebs et al. (2012)	Piva et al. (2010)
Eligibility criteria specified	Yes	Yes	Yes	Yes	Yes
Random group allocation	Yes	Yes	Yes	Yes	Yes
Concealed allocation	No	Yes	Yes	Yes	Yes
Baseline comparability	Yes	Yes	Yes	Yes	Yes
Blind subjects	No	No	No	No	No
Blind therapists	No	No	No	No	No
Blind assessors	Yes	No	Yes	No	Yes
Adequate follow-up	Yes	Yes	Yes	Yes	No
Intention-to-treat analysis	No	No	No	Yes	No
Between group comparisons	Yes	Yes	Yes	Yes	Yes
Point estimates and variability	No	Yes	Yes	Yes	Yes
Total score (/10)	5	6	7	7	6

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RESEARCH ARTICLE

Greek Physiotherapists' Perspectives on Rehabilitation Following Total Knee Replacement: a Descriptive Survey

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Abstract

Background and Purpose. In Greece, as in many countries, there is a scarcity of evidence in the type of physiotherapy services offered for the rehabilitation of total knee replacement (TKR). Despite the number of TKRs annually performed in Greece (over 10,000), there are no available clinical guidelines as to the content of best physiotherapy practice. The aim of this nationwide survey undertaken by physiotherapists treating TKR patients post-operatively was to record standard practice and services available in Greece. **Methods.** Design: cross-country survey

Ten per cent of all registered physiotherapists working in public/private sectors were recruited. The developed survey comprised of questions regarding therapists' profile, protocols implemented at different stages of rehabilitation and the aims and modalities used. **Results.** A 58.7% response rate was achieved, where 36% (47/132) of respondents were treating patients in the inpatient phase and 64% (85/132) after hospital discharge. Patients in Greece are discharged with a home-based exercise program (56.7%) and, to a lesser extent, are referred to rehabilitation centres (13.3%). Strengthening, range of movement and functionality seemed to be the primary goals especially in the inpatient phase, whereas in the outpatient phase, apart from the larger differences identified, functionality and balance training were more frequently reported. **Conclusions.** No significant variations in practice were found during inpatient rehabilitation, whilst there seemed to be diversity across outpatient physiotherapy programs. The current survey suggests that patient's general health and psychological and behavioural issues are the criteria by which physiotherapists select the volume of implemented exercise and progression. However, no specific guidelines were followed. Copyright © 2016 John Wiley & Sons, Ltd.

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Keywords

orthopaedics; physiotherapy; practice/service settings; rehabilitation services; survey

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Introduction

Recovery after total knee replacement (TKR) has generally shown consistent improvements in joint pain but with variations, in functional capability during the first year (Callahan *et al.*, 1994; Hartley *et al.*, 2002; Naylor *et al.*, 2009; Kauppila *et al.*, 2011). The quality of post-operative care and rehabilitation strategies has been suggested among other factors such as pre-operative functional status, age and other comorbidities (Fortin *et al.*, 2002; Lingard *et al.*, 2004; Jones *et al.*, 2008), to be a key determinant of the time frame of recovery, function and quality of life achieved (Roos, 2003). Whilst physiotherapy rehabilitation in the inpatient phase has traditionally focused on exercises addressing pain, strength, range of movement (ROM) and gait re-education (Worland *et al.*, 1998; Codine *et al.*, 2004; Moffet *et al.*, 2004; Dauty *et al.*, 2007), there is evidence to support accelerated rehabilitation focusing on functionality and patient mobility during the patients' time in hospital (Oldmeadow *et al.*, 2002; Thomas, 2003; Isaac *et al.*, 2007; Minns-Lowe *et al.*, 2007; Cook *et al.*, 2008; Klika *et al.*, 2009; Johnson *et al.*, 2010). The only clinical guidelines existing are published in Scotland and suggest that physiotherapy should focus on normal daily activities, ROM and muscle strength for the first 3 months (Learmont, 2000). After hospital discharge, the literature suggests that intensive protocols with emphasis on function provide the most effective benefits for patients' functional ability (Frost *et al.*, 2002; Moffet *et al.*, 2004).

Evidence for the type of services offered and the content of physiotherapy practice remains scarce within Greece, as in many other countries. This is the case despite the consistently increasing number of TKRs. The number of TKRs is estimated to be approximately 10,000 per annum in Greece (at a cost of about €7,000 per surgery) and reflecting an increase of 150% of the number from 1995 to 2005 (Xreos Zois, 2009). At the same time, while there is no consensus about optimal treatment, there is some evidence in the literature on the type and mode of exercise during TKR rehabilitation that could enhance physiotherapy practice and patients' outcome. It is therefore considered important to record how physiotherapy services work in Greece in order to promote clinical efficacy and cost utility strategies. Information about current physiotherapy practice following TKR is needed in order to know what is done and develop strategies to increase the use of evidence-based practice.

Thus, the aim of this study was to describe the rehabilitation services (both inpatient and outpatient) offered and to analyse qualitatively the Greek perspective in standard care of patients offered by physiotherapists involved in the recovery after TKR. This approach would also facilitate the identification of areas of diversity and ambiguity within physiotherapy practice needing further research.

Methods

Approval from the study was granted by the Panhellenic Physical Therapy Association (PPTA) Research Committee, the official body representing chartered physiotherapists in Greece.

Sample

This sample was a cohort selected using a randomized sampling approach from both inpatient and outpatient physiotherapy practice within Greece. Physiotherapists registered in the PPTA registry (the official body of registered physiotherapists within Greece working either in the inpatient or outpatient departments in Greece) were eligible for the survey. Exclusion criteria were treating less than 10 TKR patients annually and physiotherapists who were not registered in the PPTA registry.

For the inpatient component, randomization took place in the hospital selection, from where physiotherapists were recruited. In particular, 111 national hospitals with orthopaedic clinics were identified from the Greek Medical Directory for orthopaedic clinics (Hellenic Association of Orthopaedic Surgery and Traumatology, 2012). In order to obtain a representative sample of Greek physiotherapists, from those hospitals, 10% (11 public hospitals) were randomly selected. To obtain full geographical coverage, a stratified sampling procedure took place, where Greece was divided into two urban areas (Athens and Thessaloniki) representing the two biggest cities in Greece and four rural areas. Six geographical areas (north, north-west, north-east, central, south-east and south-west) and hospital(s) from each geographical region were randomly (via Microsoft Excel random number generator) selected according to the number of hospitals allocated in each. Thus, two hospitals were randomly selected from the north, one from the north-west, one from the north-east, four from the central, one from the

south-east and two from the south-west. The head physiotherapist in each hospital was contacted in person (by fax or post) in order to identify the number of his/her physiotherapy staff and whether specific guidelines regarding progression and discharge for TKR patients are followed in his/her facility. In cases where specific instructions were followed by all physiotherapists, a single questionnaire was delivered to the facility. If no uniform guidelines were followed, then the head physiotherapist was asked to provide email addresses/contact details from all staff (treating TKR) so as to allow delivery of questionnaires directly to each therapist. Seventy-five physiotherapists from a total of 11 hospitals were contacted in this way, and only in one hospital, uniform guidelines were followed. To minimize non-respondents, an email reminder was sent to the head physiotherapist and the department's staff within 3 weeks after the initial distribution.

For the outpatient component, as most physiotherapists in Greece work in the private sector in post-acute rehabilitation (Billis *et al.*, 2010), private physiotherapists were targeted. Thus, from a catalogue of all Greek private registered physiotherapists ($n=1,530$) accessed from the PPTA registry, a 10% random physiotherapy sample was used. Randomization was performed via Microsoft Excel random number generator. Thus, 150 randomly selected physiotherapists were contacted by email. Again, an email reminder was sent to the private physiotherapists within 3 weeks after the initial distribution.

Participants returned questionnaires by email, post or fax and were transferred into an SPSS file.

Survey design

The basic format of the selected survey instrument was initially used in a relevant study in Australia (Naylor *et al.*, 2006) and for which permission had been granted for it to be adapted in to Greek. The instrument was adapted in Greek by the primary investigator (MM) at a first stage. The translated questionnaire was then edited in its current format following in-depth discussions and clinical judgement of experienced (>10 years into research and management of knee replacement patients) physiotherapists and orthopaedic surgeons, to make it more comprehensible to the Greek culture and health-care setting. The questionnaire was then piloted in a private rehabilitation centre, where 10 physiotherapists (not included in the main sample) completed and commented on

the questionnaire before its first distribution. Following minor amendments on the word expression of a few questions, the final survey questionnaire is comprised of 22 questions of the original questionnaire by Naylor *et al.* (2006). It involved questions about the rehabilitation goals, potential factors affecting rehabilitation, outcome measures and protocols used from the inpatient phase of rehabilitation for up to 6 months post surgery. Only one question on therapists' profile (clinical experience, field of work, level of studies) was added (Doody and McAteer, 2002). The current questionnaire consisted of a combination of closed ($n=11$) and open-ended questions ($n=12$). Open-ended questions were thought as necessary, to provide respondents with freedom to expand upon answers given, improving the quality and depth of information gained and elicit a wider aspect of opinions on issues affecting practice. The inclusion of some open-ended questions was chosen as it has been proved as an effective strategy to increase the response rate (Kellerman and Herold, 2001; Nakash *et al.*, 2006). A survey outline is presented in Table 1. It was estimated that the questionnaire required 8–10 minutes to be completed. The survey was distributed from July 2011 to December 2011.

Data analysis

An SPSS data file (SPSS version 16.0, Inc., Chicago, IL, USA) was created by the primary researcher. Descriptive statistics with frequencies and percentages were used for analysis of closed questions, as most variables were either nominal or ordinal. Further cross-tabulation analysis was used in cases where physiotherapy responses needed to be further categorized according to a certain criterion (i.e. number of TKR patients seen annually). For the responses to the open-ended questions, the analysis was undertaken by two analysts, the principal investigator and a second analyst, and comprised of the following stages: (1) transcribing the information. The principal investigator read the responses and created notes on potential themes. (2) Content analysis by principal investigator and second analyst. The principal investigator and the second analyst identified and coded the data into themes and categories independently. This process was followed by the development of interpretations, main issues and concepts from the responses (Krueger, 2000). (3) Discussion between analysts. An in-depth

Table 1. Content outline of the survey questionnaire

Therapist's profile	Professional experience, specialty, academic level, N of TKR treated per year, field of work (inpatient, outpatient) (5)
Immediate post-operative (inpatient) care (N of questions)	<ul style="list-style-type: none"> • Length of hospital stay (1) • Standard physiotherapy practice (1) • Discharge criteria (1) • Referral after discharge (home with or without supervision, inpatient or outpatient) (1)
Outpatient short and long term recovery phase (N of questions)	<ul style="list-style-type: none"> • Available rehabilitation services (inpatient, outpatient, individual or group, hydrotherapy) (1) • Assessment tools (for ROM, muscle strength, function, etc.) (1) • Standard physiotherapy care (4) • Volume of exercise (frequency, duration, progression criteria) (2) • Introduction of balance exercises (timing into physiotherapy program) (1) • Expected functional ability (independency, ADL activities) (2) • Primary and secondary goals (focused to address symptoms, function, etc.) (2) • Residual problems (1)

discussion took place when the analysts' versions were revealed. There was an agreement on all main categories and on most themes (Hruschka *et al.*, 2004; Johnson and Waterfield, 2004). Irrelevant themes were removed (Krueger, 2000), and consensus was finally reached. (4) Development of the English version of the analysed transcripts. The final stage was to translate and develop the English version of all open-ended responses. The principal investigator performed the translation, and the second analyst reviewed and verified the translating themes and categories.

Results

Physiotherapists' profile

Two hundred and twenty-five survey forms were distributed in total (by email and personal contact with the head of the physiotherapy department), and 132 were returned (58.7% response rate). The response rate for the inpatient component of the sample reached a 63% (47/75), and the outpatient component reached a 57% (85/150). Of these, 47 (36%) were completed by physiotherapists who were seeing patients during the immediate post-operative inpatient phase and 85 (64%) by physiotherapists who were seeing patients after being discharged. The physiotherapists' profile is presented in Table 2.

Furthermore, when cross-tabulation analysis was performed, no noteworthy differences (to make the comparison with a *t*-test necessary) were found in the inpatient program between physiotherapists treating at least 10 and those treating more than 10 TKR patients annually.

Table 2. Physiotherapists' profile (n = 132)

		Number (percent)
Area of work	Public hospital (inpatient)	20 (15.1%)
	Rehabilitation centre (inpatient for 23/39)	39 (29.5%)
	Private physiotherapy clinic (outpatient)	34 (25.7%)
	Home visits	22 (17%)
	Community	10 (7.5%)
Clinical experience	Other, for example, academic physiotherapists	3 (2%)
	1–5 years	45 (34.1%)
	5–10 years	40 (30.3%)
Main area of specialty	Over 10 years	47 (35.6%)
	Musculoskeletal	31 (23.5%)
	Neurorehabilitation	19 (14.4%)
TKRs treated per year	Orthopaedic	12 (9.1%)
	Cardiorespiratory	5 (3.8%)
	Other	9 (6.8%)
	None	56 (42.4%)
	10	73 (55.2%)
	10–30	21 (16.2%)
	30–50	27 (20%)
	>50	11 (8.6%)

In-patient physiotherapy practice (immediate post-operative)

According to 57.4% (27/47) of physiotherapists, over half of patients (56.7%) are discharged with a home exercise program, usually unsupervised. In-patient rehabilitation, as unanimously reported, always included

gait re-education in conjunction with strengthening and ROM exercises. Table 3 presents physiotherapy interventions in the post-operative phases, whilst Table 4 presents physiotherapy discharge criteria from hospital. When physiotherapists were further asked to describe some of the standard exercises they used, they unanimously mentioned strengthening and stretching from lying or sitting positions on muscles directly acting on the knee, such as quadriceps, hip and knee flexors.

Physiotherapy practice (short-term rehabilitation period: 2–6 weeks)

Service delivery after hospital discharge

Rehabilitation according to physiotherapists' views offered after discharge either in an inpatient or outpatient basis is summarized in Table 3. Physiotherapy services available for TKR patients after discharge are presented in Figure 1. From the physiotherapists who treat patients after hospital discharge ($n=85$), 31.7% (27/85) reported that they provide sessions for a period of up to 2 weeks, 49.2% (42/85) between 2 and 6 weeks and 19.1% (16/85) for more than 6 weeks.

Rehabilitation goals after hospital discharge

During this course of management physiotherapists' goals included (1) restoration of muscle strength and

Table 4. Hospital discharge criteria

Discharge criteria	Outcome measure achieved	Percentage of respondents
ROM	Full extension, 90 flexion	20
Gait	Independent gait (40 m)	20
	Independent transfers, compliance with home exercise program	13.4
Pain	Control of pain	3.3
Stairs	Independent with stairs	10
ROM + gait + pain + stairs	All the above	23.3

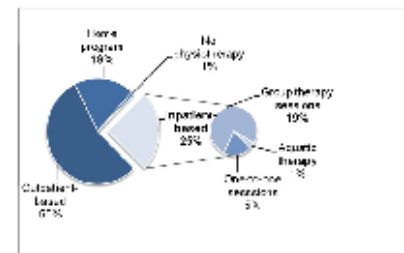


Figure 1. Physiotherapy rehabilitation services received after discharge from hospital (according to physiotherapists' views) ($n=132$)

Table 3. Physiotherapy interventions in the post-operative phases

Setting	Intervention	Percentage of respondents
Inpatient	Transfer training	93.3
	Strengthening (knee extension, knee and hip flexors)	
	Patella mobilization	
	Continuous passive motion	
	Gait re-education	
	Exercises (stretching and strengthening of knee-related muscle groups), gait re-education with crutches	
Discharge from hospital	Exercises (stretching and strengthening of knee-related muscle groups), stairs	3.3
	Closed kinetic strengthening exercises	9.5
	Gait re-education	1.9
	Functional exercises	5.7
	Closed kinetic strengthening exercises + gait re-education + functional exercises	21
	Closed kinetic strengthening exercises + gait re-education + functional exercises + balance exercises	50.7
	Closed kinetic strengthening exercises + gait re-education + functional exercises + PNF (hold-relax technique) + massage + manual therapy + electrical muscle stimulation	9.5
	Monitored home program	1.9

ROM (47.2%, 40/85), (2) improved gait (21.1%, 18/85), (3) amelioration of patients' functional status and provision of safe and ergonomic instructions (22.3%, 19/85), and (4) achievement of good balance and proprioception (9.4%, 8/85).

Factors influencing rehabilitation programs, progression and expected outcome at 6 weeks

Physiotherapists reported various factors taken under consideration in order to determine and progress the volume and intensity of exercise applied to patients (refer to Table 5). Amongst the most commonly reported influential factors for exercise progression were the patient's general health, psychological and behavioural issues, any post-operative complications occurring and surgeons' guidelines.

Outcome measures utilized

Figure 2 presents the outcome measures used by physiotherapists to assess patients' progress. As it can be seen from the graph, a significant number of physiotherapists report not using any outcome measure. However, when the frequency of specific outcome measures used (i.e. goniometer, muscle strength testing, functional measures) was further analysed among physiotherapists seeing less than 10 or more than 10 TKR patients, no noteworthy difference was observed.

Final stage of recovery—functional rehabilitation (6 weeks up to 6 months)

During this final period, physiotherapists seem to predominantly focus on improving balance and function (64.5%, 55/85), and to a lesser extent on balance and endurance (20.5%, 18/85), or gait asymmetries (6.5%, 5/85), whilst a small percentage of respondents (8.5%, 7/85) do not usually treat patients during this

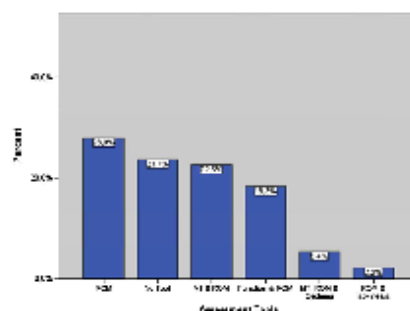


Figure 2. Assessment tools utilized in everyday clinical practice (n=132)

period (they seem to stop at 4–6 weeks). According to physiotherapists' perspectives, there is a range of residual problems determining poor outcome at this stage, including lack of full passive extension (50.6%, 43/85), quadriceps muscle weakness (22.6%, 19/85), inadequate flexion ROM (15.3%, 13/85), medical history (7%, 6/85), instability (2.4%, 2/85), swelling (1%, 1/85) and patients' fear (1%, 1/85). Table 6 presents the reasons that lead either patients or physiotherapists to end their rehabilitation program.

Discussion

This is the first cross-country survey to qualitatively assess opinions and current practice of TKR rehabilitation among Greek physiotherapists working in a range of acute, community and outpatient settings. The study is considered pragmatic, and the physiotherapy sample is believed to be representative for Greece because (1) a random sample of all registered Greek physiotherapists with full geographical representation responded to the survey, (2) physiotherapists involved had all been

Table 5. Factors affecting decision-making in volume of rehabilitation program

		Percentage of respondents
Factors affecting selection of primary program	Patient's complications and social-cognitive attitude towards rehabilitation	61.3
	Patient's general health and current medical status	29
	Surgeons' guidelines	3.2
	Patient's health insurance	6.5
Factors affecting volume of exercise being implemented	Patient's medical status and endurance	75
	Patient's effort, psychological status and muscle strength	9.8
	Patient's age and pain levels	9.8
	Patient's post-operative stage and surgeon's guidelines	5.4

Table 6. Factors implicated in ending physiotherapy rehabilitation program

Criteria for ending physiotherapy (according to patients' views)	Painless and home independence	85 (64.5%)
	Return to ADL	37 (28%)
	Prescription by orthopaedic surgeon	10 (7.5%)
Factors implicated to ending physiotherapy program (according to physiotherapists' views)	Patient's complications and motivation	74 (50.9%)
	Cost covered by public insurer	8 (6.5%)
	Complications	7 (5.4%)
	Surgeon guidelines	4 (3.2%)
	Medical history	3 (2.2%)
	All the above (except cost constraints)	20 (6.5%)
	All the above and cost constraints	16 (11.8%)

treating at least 10 TKR patients (inpatient or outpatient) annually, (3) it purposively reflects physiotherapists' perceptions (both novice and more experienced ones) in hospitals and clinics nationwide, where TKRs are performed, and (4) it encompasses rehabilitation centres and private practices, where patients are referred after hospital discharge. The outpatient physiotherapy sample used was thought to be representative as physiotherapists in Greece are mostly employed privately and without having official specialties (Billis *et al.*, 2010). The response rate for the inpatient component of the sample reached a 63% (47/75), and the outpatient component reached a 57% (85/150), which are considered acceptable (Instructional Assessment Resources, 2011).

Inpatient physiotherapy practice (immediate post-operative phase)

Rehabilitation strategies are dependent upon the constraints of health-care budgets, patient income and physiotherapy protocols (Heck *et al.*, 1992; Pearson *et al.*, 2000; Naylor *et al.*, 2009). Variations in therapists' preferences according to the health system, education and culture are also expected. Physiotherapists in the inpatient phase tend to focus on ROM, muscle strengthening and gait training. In addition, physiotherapists' duties also encompass bed mobility and transfers, activities that are usually considered to be within the field of occupational therapy (Dejong *et al.*, 2009). An older (1994) British survey from the Association of Orthopaedic Chartered Physiotherapists (AOSP) reported the type of exercises utilized, incorporating isometric quadriceps, dynamic quadriceps (0°–30°), straight leg raise and active flexion exercises (Frost *et al.*, 2002). Continuous passive motion, cryotherapy and patellar mobilizations are

other inpatient interventions reported in the current survey as well as across the literature (Smith *et al.*, 2002; Denis *et al.*, 2006) but with inconclusive results for clinical efficacy and effectiveness. Nevertheless, there is evidence to suggest that physiotherapy interventions during the inpatient phase should be more closely linked to daily activities (walking, chair rising, stair climbing) than to pure stretching and strengthening exercises, which were traditionally used for preparing patients for the home environment (Frost *et al.*, 2002; Noble *et al.*, 2005; Grotle *et al.*, 2010).

In Greece, there appears to be a variety of available discharge criteria utilized either in combination or separately (i.e. 20% of therapists reported ROM as the most important achievement, 20% prioritized short distance gait capability, etc.). The recent trend in the developed countries however is the utilization of functional discharge criteria involving transfers, personal care, ability to walk with walker/crutches for >70 m and visual analogue scale scores of <5 for activity (Husted *et al.*, 2011).

Introduction of enhanced recovery programs in inpatient rehabilitation facilities

The fast-track set-ups have optimized logistical and evidence-based clinical features (Husted *et al.*, 2008). In these set-ups, a specific protocol is followed in terms of surgical approach and rehabilitation regime. The aims of the enhanced recovery programs (ERPs) are to reduce length of stay to 2–3 days (previously reported to be on average 6–12 days) and to start physiotherapy within 24 hours post-operatively (Husted *et al.*, 2006; Husted *et al.*, 2011; McDonald *et al.*, 2012; Smith *et al.*, 2012). In Greece, the fast-track set-ups were reported to be applied in only 16.7% of cases according

to this survey but without any evidence of clinical outcome recorded. There is an emphasis lately in Denmark, Spain and UK for delivering fast-track setups (called ERPs in the UK). Further good quality randomized controlled trials are recommended before the routine implementation of ERPs within hospital and other clinical environments could be fully endorsed.

Physiotherapy practice after hospital discharge

Following hospital discharge, depending on each country's health-care resources and patient needs, clinical pathways and physiotherapy strategies involve, either outpatient physiotherapy, supervised home-based programs or no rehabilitation (self-directed) (Shepherd *et al.*, 1998; Kramer *et al.*, 2003; Moffet *et al.*, 2004; Rajan *et al.*, 2004; Lavemia *et al.*, 2006; Barrois *et al.*, 2007; Genet *et al.*, 2007; Isaac *et al.*, 2007; Mockford *et al.*, 2008; Coulter *et al.*, 2009). According to Greek physiotherapists, the majority of patients were discharged with a home exercise program, usually unsupervised, and to a lesser extent discharged to outpatient physiotherapy. Outpatient physiotherapy is usually offered by a physiotherapist who is contracted with a public health-care insurer (located either in a private physiotherapy facility or at the patient's home). Home programs were reported by physiotherapists as more convenient. Interestingly, home programs (supervised even by regular telephone appointments) are a subject of research as they are preferred by patients and are reported in some studies to be equally effective to clinic-based rehabilitation (Mitchell *et al.*, 2005; Genet *et al.*, 2007; Galea *et al.*, 2008; Mahomed *et al.*, 2008; Coulter *et al.*, 2009).

In terms of service availability after discharge, physiotherapists reported that rehabilitation is mostly offered on an outpatient basis (55.2% compared with 24.8% for inpatient rehabilitation). Inpatient rehabilitation services in Greece are mostly found in the private sector; however, finances for in-stay rehabilitation are provided partly via public health insurance. In such inpatient facilities, rehabilitation is offered either in group-based programs or one-to-one sessions with the availability for aquatic therapy. The concept of group therapy has been introduced in Greece recently. Although one-to-one therapies are identified as more targeted in the literature because patients inherently receive individualized attention, group benefits seem

to be just as efficient, enjoyable and cost-effective (Coulter *et al.*, 2009; Aprile *et al.*, 2011). In Australia and UK, post-operative rehabilitation is more often conducted within outpatient or community-based services (Lingard *et al.*, 2000; Naylor *et al.*, 2006), in contrast to the United States and Norway, where post-surgical rehabilitation takes place in transdisciplinary clinical team inpatient facilities (Dejong *et al.*, 2009; Grotle *et al.*, 2010). Services involving group therapy are delivered in Australia and England too (Naylor *et al.*, 2009; Artz *et al.*, 2013). Additionally, the literature has revealed that early home rehabilitation for patients that has been targeted effectively reduces hospital length of stay, thus bringing about savings to the care provider (Nyland *et al.*, 2011).

With post-discharge (up to 6 weeks) rehabilitation, the vast majority of Greek physiotherapists report a tendency to include functional closed kinetic chain exercises, gait re-education and balance exercises focused on function, which is consistent with recent evidence (Codine *et al.*, 2004; Mizner *et al.*, 2005; Lavemia *et al.*, 2006; Klika *et al.*, 2009; Rossi *et al.*, 2010). Neuromuscular electrical stimulation was also reported as an additional intervention for stimulating quadriceps, and it has also shown to further enhance strength and function when combined with resistance exercises (Pettersson *et al.*, 2009). There was some ambiguity among physiotherapists about the inclusion of balance exercises within the first 6 weeks post-TKR (50.7 and 21%, for and against, respectively), despite current literature supporting their inclusion in TKR rehabilitation (Gage *et al.*, 2008; Dejong *et al.*, 2009; Gauchard *et al.*, 2010; Piva *et al.*, 2010). Research on the timing of inclusion of balance exercises is needed as even in the early stages, they seem to improve functional ability with no adverse effects, that is, knee effusion (Gauchard *et al.*, 2010; Piva *et al.*, 2010; Liao *et al.*, 2013).

Outcome measures utilized

A significant proportion of physiotherapists (23.7%) reported not using any outcome measure for assessing patients' progress. Range of motion with muscle testing (22.6%) and functional outcome measures (i.e. timed up go [TUG]) have been reported (18.3%) as outcome measures used in the current survey. Therapists would benefit from the use of outcome measures that capture functional assessment in order to target patients'

program on functional needs on each stage. Indeed, functional tests such as TUG and outcome scores such as the Western Ontario and McMaster Universities Arthritis Index are the most frequently used in the literature to assess patient's mobility skills, as they are found to be valid, reliable, responsive and feasible in clinical practice (Boonstra *et al.*, 2008; Beard *et al.*, 2010).

Factors influencing rehabilitation programs, progression and expected outcome at 6 weeks

Criteria for exercise progression and exercise volume are one of the understudied aspects of rehabilitation. Physiotherapists in the current survey reported that resistance is increased according to patients' capabilities, without utilizing objective criteria. Both from this survey and from the international literature, physiotherapists do not seem to be familiar with the criteria for exercise progression. Therefore, there appears to be a need for more objective criteria that compliment exercise progression with patient capabilities. Classification of patient progress with categories such as functionally independent, those requiring supervision and those requiring constant assistance could be a helpful strategy for exercise progression (Oldmeadow *et al.*, 2002). Preliminary evidence on a high-intensity, long-duration rehabilitation program initiated after discharge indicated significant benefits on muscle strength and functional tasks such as TUG (Bade and Stevens-Lapsley, 2011). Nevertheless, progression in this latter study was again achieved subjectively (dependent upon patients' tolerance or complaints) and not on the achievement of specific milestones.

Although there are studies that highlight the importance of continuing physiotherapy after 3 months from TKR (Woolhead *et al.*, 2005; Valtonen *et al.*, 2009), in Greece, most physiotherapists usually stop physiotherapy at this stage because of patient's financial constraints or patient's motivation. This pattern of cessation of care is similar to what has been indicated in the literature (Dexter, 1992). Recovery at 6 months is reported to be substantially dependent upon pre-operative pain and function (Jones *et al.*, 2003).

The current survey highlights as main residual problems the lack of full passive extension and quadriceps weakness. At the end of the first post-operative

month, patients have been shown for the first time to perform activities of daily living activities with the least dependence compared with the initial recovery period after surgery but with the most prevalent deficits in muscle strength (up to 60% compared with the pre-surgery levels) (Mizner *et al.*, 2005; Stevens-Lapsley *et al.*, 2010). Moreover, the performance in climbing stairs and 'stand up and go' returned to pre-operative levels 2 months post surgery (Mizner *et al.*, 2005). Relevant literature highlights intensive rehabilitation programs with an emphasis on function (Ouellet and Moffet, 2002; Dauty *et al.*, 2007) to address these deficits. Therefore, maximizing functional outcome and quadriceps strength in the first month after surgery seems to be a challenging area for further research especially as both factors appear to correlate highly.

Study limitations

Although every effort was made to provide a fair Greek hospital representation, a relatively small number of hospital-based physiotherapists (26.6%) participated in the survey. Greek physiotherapists are disproportionately low in hospital-based settings (Billis *et al.*, 2010). The analysis of the sample's profile showed that a significant percentage of physiotherapy respondents (55.2%) treats just over 10 TKR patients annually. This number could be considered as relatively low. However, currently no physiotherapy specialty exists in Greece, and a physiotherapist's clinical portfolio would most likely show a large variety of patients (Billis *et al.*, 2010). Therefore, in order to minimize any possible bias, further cross-tabulation analysis was performed to compare physiotherapists treating 10 and those treating greater than 30 TKR patients annually and, interestingly, no noteworthy differences emerged. Additionally, reporting bias cannot be fully excluded as it is considered that not all professionals are willing to answer surveys or to report their views without bias. Finally, this is a survey study of clinicians based on self-reporting by physiotherapists, and therefore, the data that has been analysed represents indirect measures and not patient-specific data. Consequently, although the results provide clinically useful information, the interpretation should be made with some caution. We had initially aimed to collect information on therapist's selected dose of treatment, but this could not be determined after all.

Conclusion

This is the first Greek national survey to record physiotherapists' views on the rehabilitation process of patients undergoing TKR. Patients in Greece are described by physiotherapist to be mostly discharged with a home-based individualized exercise program. A consistency in care was described by therapists during inpatient rehabilitation, whilst there seemed to be diversity in the physiotherapy programs implemented in the short- and long-term outpatient recovery phase. Strengthening, ROM and functionality seem to be the primary physiotherapy goals. A significant number of physiotherapists reported not using any specific outcome measure for assessing patients' progress, whereas empirically based criteria (i.e. patients' medical status, endurance, muscle strength, etc.) were used. Most physiotherapists tend to stop rehabilitation at 3 months because of financial constraints or patient motivation. Future research should aim at providing guidelines regarding the application and timing of initiation of optimal dosage, type and intensity of exercise conditioning. In particular, the optimal implementation of balance-related exercises is a prerequisite for patients' functionality and reflected an area of ambiguity among the physiotherapy responses in this survey.

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The effect of total knee arthroplasty on patients' balance and incidence of falls: a systematic review

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Abstract

Purpose Despite the high incidence of falls in patients with OA, few studies have explored whether falls risk is affected after patients undergo total knee arthroplasty (TKA). Therefore, the aim of this systematic review was to identify the extent of the effects of TKA on balance and incidence of falls by critically reviewing the available literature.

Methods A systematic review of published literature sources was conducted up to March 2014. All studies assessing balance and incidence of falls after TKA (without physiotherapeutic intervention) were included. The methodological quality of each study was reviewed using the Critical Appraisal Skill Programme tool.

Results Thirteen studies were included, comprising of ten cohort studies (Level II) and three studies with Level of evidence III.

Conclusions Findings provide evidence that TKA improves significantly single-limb standing balance (~60%) and dynamic balance up to 1-year following surgery (Level of evidence II). Moreover, TKA influences positively fear of falling and incidence of falls by switching 54.2 % of pre-operative fallers to post-operative non-fallers (Level of evidence II–III). It is highlighted that knee extension strength,

proprioception and symmetrization of postural strategies have not fully recovered post-TKA and influence balance performance. Clinically, these persistent deficits need to be mitigated by physiotherapy even before TKA takes place.

Keywords Balance control · Falls · Falls risk · Total knee arthroplasty · Systematic review

Introduction

Balance is essential for maintaining postural stability while performing functional activities and for fall avoidance [48]. Balance (dynamic and static) is a complex function which requires integration of sensory information regarding the position of the body and the ability to make appropriate motor response to body movement [22]. More precisely, it depends on sensory inputs from somato-sensory (proprioception), visual and vestibular systems [5], as well as, response of muscles. Static balance refers to maintaining equilibrium while standing in one spot, whereas dynamic balance involves motion and is defined as maintaining equilibrium during locomotion [37]. Falls and loss of balance most commonly occur during movement-related tasks such as walking and less frequently during static activities [23].

Balance deficits have been identified as one of the integral components impairing daily living in patients with knee osteoarthritis (OA) and are associated with an increased risk of falls and poor mobility [59]. Approximately 60–80 % of patients with knee OA report knee instability, which causes activity limitations [14, 44]. Osteoarthritis has been shown to be an important risk factor for falls with more than 40 % of all patients and 64 % of female patients, with OA reporting falls within a year in America [18, 59]. Potential mechanisms causing balance impairments in this population

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have not yet been fully elucidated [13, 25, 39, 50, 51]. Age-related impairments in the capacities of physiological systems controlling balance is one of the potential contributory mechanisms [47]. Proprioceptive impairment of the joint sometimes precedes knee OA and deteriorates further the degeneration associated with the disease [46]. Knee pain and quadriceps' weakness are associated with increased postural sway [8, 20, 27, 30]. However, while total knee arthroplasty (TKA) (treatment of choice for end-stage OA) aims to relieve pain, correct deformities and restore loco-motor function, it is not established whether it has an effect on patients' balance and incidence of falls. The literature suggests that patients with knee OA undergoing TKA will often present with a substantial loss of balance control and proprioceptive acuity that is frequently precipitated by a lack of confidence [13, 25, 28, 31, 34, 35, 39, 42, 51]. Despite the high incidence of falls in this population, there is a scarcity of investigations in the literature focusing on the risk of falls and subsequent impairments in function for patients with knee OA after undergoing TKA.

Chronic knee OA pain is reduced after TKA, but little is known about the recovery of proprioceptors, neuromuscular control, joint-related stability and also about each aspect's natural recovery after surgery. Conversely, asymmetrical gait patterns and postural sway (in the coronal plane) combined with increased forward trunk movement (in the sagittal plane), observed especially in the early post-operative period, cause balance difficulties and increased risk of falls [10, 19, 24].

Residual physical deficits have been observed up to 7-year following TKA, with significant impact on functional status (i.e. postural stability, walking speed, stair ascent/descent) [6, 17, 36, 41, 55, 56, 60, 61]. In turn, decreased muscle strength, ROM and altered movement patterns evident post-surgery affect the sensory and mechanical function of the joint. Byrne & Prentice [7] reported that TKA affects the ability of patients to step over an obstacle.

Thus, there are a number of factors that may influence the effect of TKA on balance and consequently the incidence of falls. Understanding of the mechanisms associated with the recovery of the systems that control balance and the specific residual problems after surgery may ultimately help to enhance the design of rehabilitation programmes using approaches that are justified by scientific evidence. Based on this rationale, the novel aim of this study was to conduct a systematic review in order to identify the effects of TKA on balance and on the incidence/ risk of falls.

Materials and methods

The electronic databases: the Cochrane Central Register of Controlled Trials (Cochrane Library), MEDLINE,

EMBASE (via ProQuest), Biomed Central, CINAHL (via EBSCO host) and Physiotherapy Evidence Database (PEDro) were searched from January 1995 to the present (September 2014). The MEDLINE Mesh keywords used were: Balance OR stability OR postural control OR falls AND knee replacement OR knee arthroplasty in the title or abstract or keywords of the studies. Clinical trials published in the English language were included. The reference lists of all eligible papers were also screened to identify any studies that had been missing from the databases. The format of the search terms was modified appropriately for use in each database searched.

Eligibility assessment was performed independently in a standardized manner, and disagreements amongst reviewers were resolved by consensus. Therefore, studies were included if they fulfilled the following 4 criteria:

1. Participants underwent primary TKA.
2. No physiotherapeutic intervention/rehabilitation was involved after hospital discharge for TKA.
3. Balance, postural control and/or falls incidence was/ were used as outcome measure/s.
4. The full paper was published in the English language.

Studies included cross-sectional, cohort and randomized controlled trials (RCTs), but excluded case studies. All cadaver or animal studies were excluded. Moreover, studies with samples involving patients with rheumatoid arthritis (RA) were excluded.

Two evaluators independently selected the studies based on titles and abstracts and excluded those not related to the subject. The full text was obtained for all papers that were considered potentially relevant. Once collected, these were reviewed by both reviewers to determine whether eligibility criteria had been fulfilled. The studies finally included were analysed according to a certain structure: author/year, sample, study design, assessment outcome measures, timeline, physiotherapy treatment, equipment and effects. The selection criteria were applied to the title and to the abstract of all articles retrieved in the search of the literature. The full text articles not excluded in the initial selection process were then evaluated for inclusion using the same eligibility criteria.

The methodological quality of each study was evaluated according to the Critical Appraisal Skills Programme (CASP) tool. This appraisal tool has been widely used in systematic reviews and is recognized to be a valid tool. The tool uses a set of 11 questions to evaluate domains such as: study design, appropriateness of design, randomization method, blinding, accuracy in the description of the sample recruitment, treatment effects, finding' interpretation.

In the first stage, a descriptive review of studies assessing balance and falls incidence in patients after knee replacement was undertaken (Table 1).

In the next stage, the analysis involved a critical appraisal process of the studies according to the CASP tool to determine the methodological quality and to summarize findings (Table 2). Strong evidence was indicated by the availability of consistent findings in two or more high quality RCTs, moderate evidence by a high quality RCT, or two or more low quality RCTs. Limited evidence was indicated by cohort studies and case-control studies.

All data extracted from the studies were analysed independently by each reviewer (MM and RP) and subsequently discussed. In any case of disagreement, further discussion was performed with a third reviewer (NG) to reach a mutual agreement.

Statistical analysis

Studies comparing static and dynamic balance pre- and post-TKA with comparable outcome measures were identified and pooled through a meta-analysis. Heterogeneity was assessed using the I^2 measure. It was considered that $I^2 < 60\%$ was acceptable to pool data [21]. The statistical significance was considered at $p < 0.05$. Qualitative review of the evidence was performed when the studies could not be pooled.

Results

Search results

A total of 276 citations were identified by the search strategy, summarized in Fig. 1. Initially, 237 studies were eliminated because the title, abstract or keywords did not match the proposed theme. Of the 36 that remained, 22 were eliminated due to the non-English language used. Therefore, due to the other aforementioned exclusion criteria, 13 studies were deemed eligible and were finally included in the review.

Cohort characteristics

In all studies, patients had primary OA (grade III–IV according to the Kellgren and Lawrence system) and fulfilled criteria to undergo TKA. All knees were implanted with the same type of cemented prosthesis (unilaterally or bilaterally). No patellar component was inserted in any of the studies.

A description of the included studies, with the outcome measures used, the follow-up period and the clinically relevant findings is presented in Table 1.

Outcome measures

All studies used validated measures to assess balance parameters [48]. Functional stability limits, reactive

control, control of balance during an active task, standing balance are all balance components being investigated in the studies, all linked with balance-related falls [29].

Regarding the incidence of falls after TKA, five studies included risk of falls assessment in addition to balance assessment [16, 29, 53, 54, 60]. One study used the short form of the Physical Profile Assessment (PPA) that encompasses five tests (proprioception, knee strength, postural sway in two directions and reaction time) to assess risk of falls [29].

Critical appraisal of studies' methodological quality

Of the 13 studies included in the systematic review, 10 followed a cohort design (Level IIc), seven of which included a control group [11, 12, 29, 32, 43, 57, 60]. Three studies were observation case-control studies (Level III) [15, 16, 54]. The quality of the studies has been assessed as although all studies satisfied a similar number of criteria, their methodologies varied substantially.

All studies offered clearly defined research questions, population characteristics and methods of assessing balance (Table 2). In 5 studies [12, 45, 53, 54, 60], a number of participants were lost to follow-ups, implying potential bias. Only 3 studies had based their sample on a power calculation analysis [12, 53, 54]. In relation to interpretation, all studies discussed their findings based on current evidence. Generalization of findings was feasible in only 2 studies [12, 54], as in the other ones, either the sample size was not sufficient, or control group was absent.

Synthesis of results

Static balance post-TKA

Patients with TKA presented with 67 % less ($p < 0.05$) mean single-leg stance duration than that of healthy controls [33]. Postural sway in static single-limb stance was improved -60% 11 days after TKA compared to pre-surgery [12]. When balance was perturbed in a sagittal plane, no difference in balance control was observed between TKA patients and age-matched controls [15]. However, when balance was perturbed in the frontal plane, control of balance showed statistically significant impairment in TKA patients compared to controls [16].

Dynamic balance post-TKA

During a dynamic task, patients with bilateral TKA present with a mean obstacle avoidance success rate that was 32 % less than that of the control group [33]. During tasks such as stepping down, lateral steps, obstacle crossing, the success rate was increased after TKA. However, statistically

Table 1 Description of the included studies in the systematic review investigating balance and risk of falls in TKR patients

Sample	Outcome measures	Timeline	Study findings	Clinically relevant findings to balance and falls
Cho and Hwang [12]	<p><i>N</i> = 11 (11F) No CG Age: 61.7±7.3 Inclusion: Radiographic varus deformity & medial compartment OA degeneration undergoing TKR</p> <p>EG: <i>n</i> = 8 (2 M, 6F) Age: 62.9±6.0 CG: <i>n</i> = 3 (5 M, 4F) Age: 62.1±5.6 Inclusion: post-TKR patients, first right TKR, at least 6 months after surgery</p>	Pre-TKR and 11-day post-TKR	<p>Improvements (~60%) in SLSB in patients with varus OA knees 11-day post-TKR</p> <p>Poor pre-TKR SLSB associated with better SLSB post-TKR</p> <p>Dynamic balance not impaired in EG vs CG in sagittal plane</p> <p>Whole body COM displacement not different between groups vs joint angle displacement and EMG => different strategy to maintain balance from CG</p> <p>EMG and kinematic responses in EG are bilateral despite unilateral joint disease</p>	Improvement in SLSB post-TKR
Gageet al. [15]	<p>EG: <i>n</i> = 8 (6F) Age: 62.9±6.0, CG: <i>n</i> = 9 (4F) Age: 62.1±5.6 Inclusion: post-TKR patients, first right TKR, at least 6 months after surgery</p>	At least 6 months post-TKR	<p>Dynamic balance control impaired in EG vs CG in frontal plane</p> <p>Increased COM displacement in EG vs CG</p> <p>Differences in joint angle displacement and EMG of EG vs CG => different strategy to maintain balance from CG</p> <p>EMG and kinematic responses amongst patients are bilateral despite unilateral joint disease</p>	No difference between groups in dynamic balance in sagittal plane
Gageet al. [16]	<p>EG: <i>n</i> = 8 (6F) Age: 62.9±6.0, CG: <i>n</i> = 9 (4F) Age: 62.1±5.6 Inclusion: post-TKR patients, first right TKR, at least 6 months after surgery</p>	At least 6-month post-TKR	<p>EMG and kinematic responses with rotation of frontal plane perturbation platform</p>	Impaired dynamic balance of EG vs CG in frontal plane
Levinger et al. [29]	<p>EG: <i>n</i> = 35 (16F) Age: 67±7, CG: <i>n</i> = 27 (14F) Age: 65±11 Inclusion: patients with knee OA who could walk independently for 45 m undergoing TKR</p>	Pre-TKR & 4-month post-TKR	<p>QoL; WOMAC; Incidental and Planned Activity Questionnaire (IPAQ), Falls Efficacy Scale (FES-1), Physiological Profile Assessment (PPA) for falls risk</p>	Increased risk of falls in EG compared to CG. Impaired SLSB of EG vs CG
Mandeville et al. [32]	<p>EG: <i>n</i> = 19 (14F) Age: 64.0±7.74, CG: <i>n</i> = 21 (13F) Age: 63.1±4.26 Inclusion: end-stage OA undergoing TKR</p>	Within 2 pre-TKR weeks and 6-month post-TKR	<p>VAS; WOMAC; obstacle overcomet; kinematic displacement on force platform during gait</p>	Improved dynamic balance in EG vs controls

Table 1 continued

Sample	Outcome measures	Timeline	Study findings	Clinically relevant findings to balance and falls
Mauer et al. [33]	<i>n</i> =29 (9F) Age 72, 6±5 A, bilateral (BL) TKR, CG; <i>n</i> =27 (7F) Age 70, 6±5.5. Inclusion: knee OA who could climb stairs, rise from a chair, have 20/40 vision or better undergoing TKR	EG tested post-TKR: 2.75±1.29 (range 1–5 years)	EG SLSB duration was 67% less than the CG EG 30% less obstacle avoidance success rate than the CG	Impaired SLSB in EG vs CG. Increased risk of falls in EG vs CG
McChesney and Woodroff [11]	<i>N</i> =22 Age ≥70 Groups: knee OA, mild OA, patients undergoing TKR	Not stated	Able & knee groups with lower TIPS showed increased COP variance. Post-TKR patients showed no reductions in any aspect of postural control. No statistically significant improvement in posturographic parameters in EG1 & EG2 vs CG group at follow-ups post-TKR Statistically significant improvement in pain and function of EG1 & EG2 post-TKR	No difference on SLSB or dynamic between groups Standing balance did not show a clear trend towards improvement in TKR patients post-TKR
Quagliarella et al. [43]	<i>N</i> =240 (142F), EG1: <i>n</i> =81 THR Age range: 40–80/42–82 years EG2: <i>n</i> =100 TKR Age range: 48–80/48–79 years CG: <i>N</i> =59 Age 67.4±5.9. Patients able to stand without support for 120 s.	Pre-op; 6 months & 12 months post-TKR	Posturography on force plate	Standing balance did not show a clear trend towards improvement in TKR patients post-TKR
Schwartz et al. [45]	<i>n</i> =62 (52F) mAge: 73 (r: 57–83). Inclusion: Knee OA patients able to walk & follow simple instructions undergoing TKR	Pre-TKR & 12-month post-TKR	Dynamic & static Balance with force platform; TUG; SF-36	Significant improvement in dynamic and functional balance; NS for static balance
Swinckels et al. [54]	<i>n</i> =99 (63F) Age 73.4±4.9 Inclusion: primary TKR	Pre-TKR and 12-month post-TKR	falls number; WOMAC; ABC; UK; GDS	Significant switch of pre-TKR fallers becoming non-fallers post-TKR
Swinckels and Allain [53]	<i>n</i> =22 (16F) Age 74.8±5.2y Inclusion: primary TKR.	2–50 day pre-TKR (mean: 23) 143–218 day post-TKR (mean: 183)	falls number; WOMAC; ABC; GDS; BBS; TUG	Functional balance improved post-TKR in 54% of patients post-surgery 50% of patients exceeded MDC for TUG post-surgery Findings on fallers are restricted by the small sample size

Table 1 continued

Sample	Outcome measures	Timeline	Study findings	Clinically relevant findings to balance and falls
Viron et al. [57] 20 patients EGI: N=8(3F) Age 67 (46–77) CG N=12(6F) Indusion: Unilateral TKR	VAS; kinetocokinematics in side step on force platform	15-day pre- and 12-month post-TKR	Improved VAS Presented with more symmetrical posturo-motor strategies Evidence of persisting posturo-motor impairments of EG vs CG Increased SLSB in operated limb in EG	SLSB improved in operated limb during tasks
Yakhdani et al. [60] EG1: n = 14(10F) Age 61.6±10.0 CG: n=12(7F) Age 62.0±12.6 Indusion: Unilateral knee OA undergoing TKR, sufficient physical condition	Dynamic balance; falls; gait variability	pre-TKR, at 6 weeks, at 6- and 12-month post-TKR	EGI: increase of maximum gait speed post-TKR Decreased gait variability of EG post-TKR in relevance to CG Increased stability post-TKR	Reduced risk of falls Recovery of dynamic balance

CG control group, EG experimental group, TKR total knee replacement, mCTSIB modified clinical test for sensory inter- and balance, TTPS threshold of passive joint position sense, ABC-UK activity balance confidence scale, GDS geriatric depression scale, BBS berg balance scale, MDC minimal detectable change, COP centre of pressure, COG centre of gravity, TUG timed up and go test, NS non significant

significant conservative strategies (slower speed, shorter stride length, shorter base of support) ($p < 0.05$) were adopted resulting in increased duration of each task of up to 30 % [12, 32, 33, 45, 57].

Falls risk

After TKA, less than half (45.8 %) of pre-operative fallers continued to fall [54]. Patients who fell pre-operatively had an eightfold increase in the risk of post-operative falling [54]. A lower risk of falls was reported in 4 studies after surgery [29, 53, 54, 60]. In the PPA risk of falls, the only parameters that reached statistical significance were proprioception and knee extension strength 1-year post-surgery [29]. Balance confidence (ABC-UK) was significantly improved after TKA; however, results remained statistically significant ($p < 0.001$) only in patients with no history of falls pre-operatively [54]. Patients with higher ABC-UK pre-operatively reduced the odds of becoming a faller for up to 1 year post-operatively by 98 % (95 % CI 0.96–1.01, $p = 0.04$) [54]. Berg Balance Scale scores of fallers and non-fallers were similar both before and after TKA, although scores were improved more than the minimal detectable change (MDC) in 41 % of TKA patients [53].

Discussion

The most important finding of the present study was that TKA influences positively (a) fear of falling and incidence of falls by switching 54.2 % of pre-operative fallers to post-operative non-fallers and (b) balance for up to 1-year following surgery. The rationale for the study was that by analysing the available literature, an understanding might be promoted of how mechanisms controlling balance, compensate or respond after surgery, and in which timeline this occurs.

Thirteen studies fulfilled criteria that had been set and were ultimately used in the analysis. No study involving post-hospital discharge physiotherapy intervention or, any other type of rehabilitation training, which might otherwise confound the extent of the isolated influence of surgery was included in this review. Despite a large number of studies in this field, very few offered a high level of evidence (Level of evidence < IIc). The sample in the studies comprised of 652 individuals in total (167 being controls), with a mean age of 71.4 years; recruited patient characteristics were typical of middle-aged individuals undergoing TKA for knee OA and were therefore considered to be representative of TKA population. The methodological quality of the studies, as assessed by the CASP scale, was acceptable. However, due to variability in sampling procedure and the absence of power calculation analysis in most studies,

Table 2 CASP Checklist for the studies included in the current systematic review

	Cho et al. [12]	Gage et al. [15]	Gage et al. [16]	Lewing et al. [29]	Mandeville et al. [32]	Mauer et al. [33]	McChesney and Woodcock [11]	Quagliariella et al. [43]	Schwartz et al. [45]	Swinkels et al. [54]	Swinkels et al. [53]	Viton et al. [57]	Yakhlani et al. [60]
Clearly focused issue	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Acceptable patient recruitment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Randomized patient assignment	NA	✓	NA	✓	✓	NA	✓	✓	NA	✓	✓	NA	NA
Sample based on power calculation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patients fulfilled follow-ups	✓	✓	NA	✓	✓	NA	✓	✓	✓	✓	✓	✓	✓
Patients, examiners blinded	✓	✓	✓	✓	✓	NS	NS	✓	NA	✓	✓	NS	NS
Similarity of patients/groups	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	✓	✓	✓
Equal treatment of patients/groups	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clearly specified outcome measures	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Large treatment effect	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2 continued

	Cho et al. [12]	Gage et al. [15]	Gage et al. [16]	Levinger et al. [29]	Mandeville et al. [32]	Mauer et al. [33]	McChesney and Woodcot [11]	Quang-arellinet al. [43]	Schwartz et al. [45]	Swinsels et al. [54]	Swinsels et al. [53]	Vitton et al. [57]	Yakelham et al. [60]
Estimate treatment effect (CI)	✓	NS	NS	✓	✓	✓	✓	✓	✓	✓	NS	NS	NS
Appropriate results analysis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Combining factors listed	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Appropriate interpretation of results	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Generalization of results	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Applicable to clinical practice	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Results coincide with relevant literature	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Our evaluation	Reasonable. Short-term follow-up	Reasonable. Potential bias due to small sample size	Reasonable. Potential bias due to small sample size.	Good	Good	Good	Reasonable. CI not reported.	Outcome measures used not recommendable for TKA.	Reasonable. Potential bias due to losses to follow-up	Reasonable. Considerable losses to follow-up	Reasonable. Potential bias due to small sample size	Reasonable. Potential bias due to small sample size	Reasonable. Potential bias due to small sample size

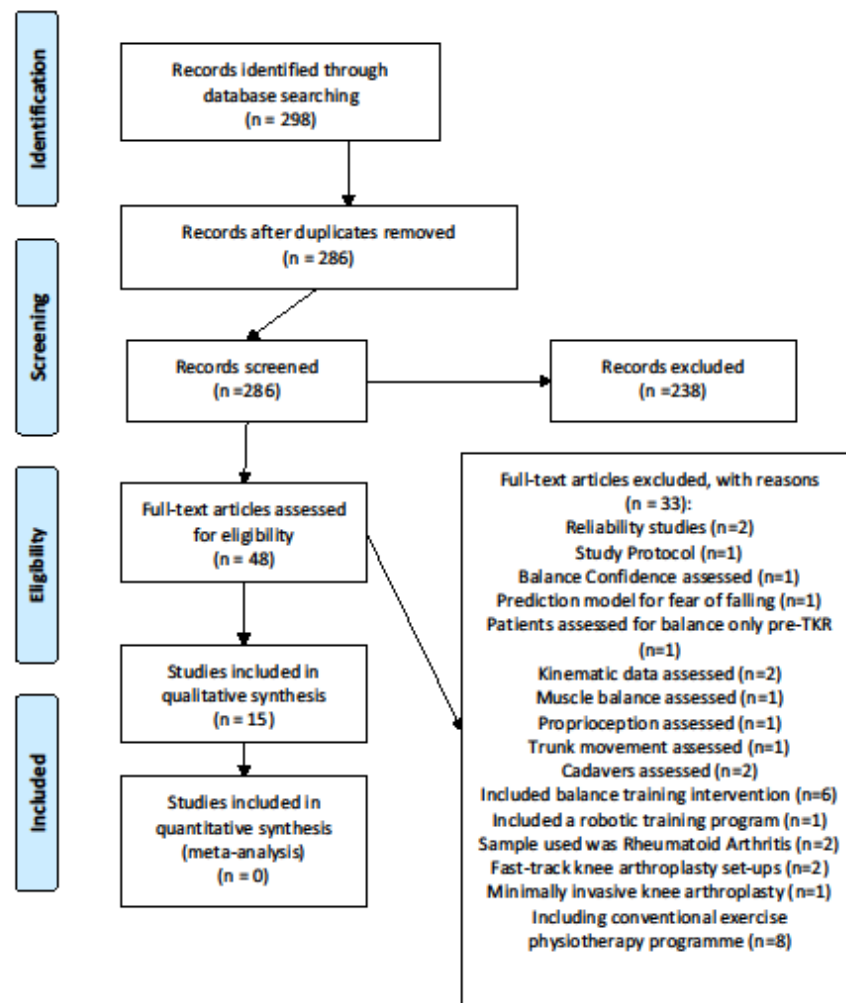


Fig. 1 PRISMA Flow Diagram to depict search strategy results. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred reporting items for systematic reviews and

meta-analysis: the PRISMA statement *PLoS Med* 6(6): e1000097. doi:10.1371/journal.pmed1000097

external validity and therefore generalizability have been limited. Major drawbacks in the studies were the lack of randomization and the lack of a control group in some studies.

Regarding the balance effects found in most studies, there was a significant balance improvement ($p < 0.001$) in both tasks and confidence after TKA compared to the

pre-operative state. While balance and sensori-motor performance were not fully restored after TKA, postural responses began to normalize in both quiet stance and dynamic tasks [32, 33, 57]. Static balance did not show a clear trend towards improvement [43]. Single-leg standing balance improved up to 60 % post-TKA, but remained poorer than age-matched controls for up to 1 year [12, 29, 33, 45, 57].

Dynamic and functional balance was found to be improved 6-month post-surgery but again not fully recovered compared to age-matched controls [32, 45, 53, 54, 60].

In studies investigating balance and postural control, the clinically relevant outcome would be patients' reported falls. A 24.2 % post-operative falls rate for TKA patients was reported up to 1 year, which is less than current estimates (33 %) for community dwelling older people [53, 54]. The rate although reduced remained as high as 45.8 % for individuals identified as fallers prior to surgery. Nevertheless, there was a significant switch of fallers' pre-TKA who became non-fallers after TKA (54.2 %) [54]. At least one fall in the first year post-TKA was recorded for 48 % of the surgical group compared with 30 % of the control group [29]. Following TKA, there was a 27 % reduction in the number of patients exceeding the cut-off point of 14 s in Timed Up and Go (TUG) [53, 54]. This time cut-off point has been proposed as a criterion for ruling out a high risk of falls in older adults [47]. Therefore, although the likelihood of falls seems to decrease after TKA, there is still a considerable amount of falls recorded post-TKA.

During TKA, the replaced knee is deprived from a variety of key proprioceptors, which have been resected (ACL, cartilage, menisci, etc.). Moreover, oscillations used by the knee joint to regulate postural control are unlikely to reach a detectable threshold by sensory receptors in the replaced knee [9]. Presumably, extra-capsular proprioceptors need to compensate for the loss, and in order to maintain stability and balance, albeit at reduced levels of capability [1, 58]. Different types of prostheses and retention of the PCL also have an impact in joint translation and mobility components [2, 4, 49]. However, different type of surgery techniques (posterior stabilization versus posterior cruciate ligament-retained) has shown contradictory findings on whether they influence balance and proprioception [3, 5, 52]. The addition of a patellar (prosthetic) component may further influence afferent sensory input; however, no relevant study was identified in the literature. Skinner *et al.* [49] suggested that the loss of proprioception due to arthritis was not improved by surgery. By contrast, Barrett *et al.* [4] claimed that when joint alignment and the 'joint space height' are reconstituted, the sense of position is improved, indicating that the reloading of lax collateral tissues at the time of the operation may be beneficial. Moreover, it has been shown that soft tissue balance (length-tension relationships for PCL and collateral ligaments) after surgery in both flexion and extension is important for allowing satisfactory post-operative knee proprioception [4]. Any difference in the tension of the medial and lateral collateral structures may therefore be perceived as a varus or valgus movement of the leg and may produce an antagonistic and corrective action from the hamstrings and quadriceps muscle groups, thus affecting proprioception [4]. Taking into account all the above literature, a number of

factors could intrude as a result of surgery that could actually have an impact on patients' neuro-sensory performance.

Bilateral postural responses after perturbation differ between TKA patients and age-matched controls. These differences are mostly observed in activation latency of muscles acting on the knee and in subsequent knee joint kinematics (reduced knee extension), suggesting a central postural re-organization process to protect against overly stressing the joint [15, 16, 32, 57, 60]. During walking, variability in knee kinematics is reduced and local dynamic stability again seems to be gradually restored [60]. Therefore, the mild improvements observed in balance following TKA may result from the retensioned capsuloligamentous structures and reduced pain and inflammation [52]. Patients post-operatively tend to normalize their weight distribution and develop more symmetrical posturomotor control.

Implications for clinical practice

Clinically, from a surgery perspective, correcting knee joint alignment and specifically varus deformity post-TKA has been shown to improve balance [12]. Considering the catastrophic consequences of peri-prosthetic fractures after a patients' fall, 3D evaluations of the alignment and computer-assisted gap-balancing techniques, than conventional techniques of TKA, may produce more advantageous balance effect [26, 40]. The clinical relevance regarding rehabilitation is that patients' training should involve rehabilitative strategies in static and dynamic tasks to achieve symmetrical weight distribution, implemented both pre- and post-TKA. Interestingly movement and weight distribution symmetry training, via the use of biofeedback, was recently introduced in the literature [62]. At the moment, there is only preliminary evidence to underpin the use of targeted sensori-motor elements within a physiotherapy programme [38]. Bilaterally observed impairments indicate that rehabilitation should include balance exercises involving both single- and double-leg stances to provoke overload and adaptation and prevent falls. Balance perturbation tasks can be more targeted towards frontal plane provocation and less in the sagittal plane [15, 16]. Moreover, knee strength and proprioception showed statistically significant improvement after TKA, whereas postural sway with eyes open and reaction time did not [29]. Finally, physiotherapy programmes should mostly incorporate the influential factors of falls (i.e. knee strength, proprioception and balance exercises with eyes closed).

Several limitations need to be considered when interpreting the findings of this review. Because of the methodological heterogeneity across the study designs (i.e. in methodological outcome measures and timing of measurements), results from a potential meta-analysis (with an $I^2 > 85\%$) would not have added consistency of evidence. Furthermore, due to methodological flaws across the studies, the level of evidence was not

high enough to allow the generalization of results. More studies with robust methodologies are needed to investigate the effect of TKA on balance and falls incidence.

Conclusions

The findings of this systematic review provide moderate evidence to support that TKA influences balance positively for up to 1-year following surgery. Studies offering Level of evidence II showed up to 60 % improvement in standing balance as early as 11-day post-TKA. Moreover, TKA influences positively fear of falling and incidence of falls by switching 54.2 % of pre-operative fallers to post-operative non-fallers (Level of evidence II–III). Patterns of change (acute and chronic) and congruence amongst the interpretation of findings from the reviewed papers endorse a conceptual framework for the knee undergoing TKA surgery. The framework supports that knee extension strength, proprioception deficits and compensatory postural strategies are persisting after surgery and are acting as the potential factors contributing to why balance and falls might be linked and only partially restored after TKA.

Compliance with Ethical Standards

Conflict of Interest No conflict of interest for any author exists.

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Informed consent This is a systematic review so the informed consent is not applicable.

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Does enhanced sensori-motor training affect functional and balance performance on patients following total knee replacement? A single-blind randomised controlled trial

Journal:	<i>Clinical Rehabilitation</i>
Manuscript ID	CRE-2017-6025.R2
Manuscript Type:	Original Article
Keywords:	total knee replacement, Balance, Proprioception, Rehabilitation, functional performance
Abstract:	<p>Objective: To assess the effects of enhanced sensori-motor exercise training compared to functional exercise training (usual care) after total knee replacement.</p> <p>Design: A single-blind randomised controlled trial.</p> <p>Setting: GR Orthopedic University Hospital of Rion, Patras.</p> <p>Subjects: Fifty-two patients electing to undergo total knee replacement.</p> <p>Outcome Measures: The primary outcome measure was the Timed Up and Go Test and the secondary outcomes were balance, joint position error, the Knee Outcome Survey Activities of Daily Living Scale and pain (Visual Analogue Scale). Patients were assessed on 3 separate occasions (pre-surgery [0 weeks]; 8 and 14 weeks post-surgery).</p> <p>Intervention: Patients were randomised to either enhanced sensori-motor exercise training [intervention] or functional exercise training [control].</p> <p>Both groups received a 12-week home-based programme prescribed for 3-5 sessions/week (35-45 min).</p> <p>Results: Changes in group mean scores favour the enhanced sensori-motor exercise training compared to control group: Timed Up and Go Test (7.8 ± 2.9 vs 4.6 ± 2.6 s); balance ($2.1 \pm 0.9^\circ$ vs $0.7 \pm 1.2^\circ$); joint position error ($13.8 \pm 7.3^\circ$ vs $6.2 \pm 9.1^\circ$); Knee Outcome Survey Activities of Daily Living Scale (44.2 ± 11.3 vs 26.1 ± 11.4); pain (Visual Analogue Scale) (5.9 ± 1.3 vs 4.6 ± 1.1). Patterns of improvement for the enhanced sensori-motor exercise training group over time were represented by a relative effect size range of 1.3 to 6.5.</p> <p>Conclusions: Overall, the magnitude of improvements in sensori-motor function endorses using enhanced sensori-motor exercise training as an effective mode of knee replacement rehabilitation.</p>

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Early self-managed focal sensorimotor rehabilitative training enhances functional mobility and sensorimotor function in patients following total knee replacement: a controlled clinical trial

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Elias Tsepis¹ and John Gliatis⁴

Abstract

Objective: To assess the effects of early self-managed focal sensorimotor training compared to functional exercise training after total knee replacement on functional mobility and sensorimotor function.

Design: A single-blind controlled clinical trial.

Setting: University Hospital of Rion, Greece.

Subjects: A total of 52 participants following total knee replacement.

Outcome measures: The primary outcome was the Timed Up and Go Test and the secondary outcomes were balance, joint position error, the Knee Outcome Survey Activities of Daily Living Scale, and pain. Patients were assessed on three separate occasions (presurgery, 8 weeks post surgery, and 14 weeks post surgery).

Intervention: Participants were randomized to either focal sensorimotor exercise training (experimental group) or functional exercise training (control group). Both groups received a 12-week home-based programme prescribed for 3–5 sessions/week (35–45 minutes).

Results: Consistently greater improvements ($F_{2,98} = 4.3$ to 24.8 ; $P < 0.05$) in group mean scores favour the experimental group compared to the control group: Timed Up and Go (7.8 ± 2.9 seconds vs. 4.6 ± 2.6 seconds); balance ($2.1 \pm 0.9^\circ$ vs. $0.7 \pm 1.2^\circ$); joint position error ($13.8 \pm 7.3^\circ$ vs. $6.2 \pm 9.1^\circ$); Knee Outcome Survey Activities of Daily Living Scale (44.2 ± 11.3 vs. 26.1 ± 11.4); and pain (5.9 ± 1.3 cm vs. 4.6 ± 1.1 cm). Patterns of improvement for the experimental group over time were represented by a relative effect size range of 1.3–6.5.

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Conclusions: Overall, the magnitude of improvements in functional mobility and sensorimotor function endorses using focal sensorimotor training as an effective mode of rehabilitation following knee replacement.

Keywords

Total knee replacement, balance, rehabilitation, functional performance, sensorimotor training

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Introduction

Despite partial improvements in functional mobility and balance, the rate of falls remains high (~45%) for patients following total knee replacement.¹ The latter partial restoration in sensorimotor function, including proprioception, postural control, and dynamic balance,¹⁻³ may persist long after surgery unless it can be targeted and counteracted effectively by novel rehabilitation.⁴

Neuromuscular rehabilitation techniques aiming at increased proprioceptive input to improve motor response in dynamic environments have received increasing therapeutic attention in recent years.⁵ This focal training is broadly known as sensorimotor training. It typically comprises stimuli for muscular strengthening and for improved control of movement by means of enhanced regulation of motor-unit recruitment by the central nervous system.⁵⁻⁷ Early adoption of focal sensorimotor training has been shown to promote safe post surgery milestones of functional recovery compared to contemporary functional therapy.^{8,9} However, its optimal delivery characteristics and efficacy remains partially unresolved due to the ongoing experimental design of the study.⁴ Thus far, the contributing evidence has not included sufficient control for the corresponding volume of training between conditions. Furthermore, no previous study has sought to investigate the effectiveness of early implementation of focal sensorimotor rehabilitative training within environments in which the preferred mode of delivery increasingly requires self-managed care by patients.^{10,11}

Given the above factors, the purpose of this study was to compare the effects of focal sensorimotor and functional (usual care) exercise training

on patients' functional mobility and sensorimotor function following total knee replacement. Both rehabilitation programmes were adopted early after surgery by patients, matched for prescribed exercise volume, and delivered by means of self-managed care.

Methods

A single-blind (group allocation concealed from participants) controlled clinical trial was undertaken at a primary care university hospital in Greece (International Standard Randomized Control Trial Registration: ISRCTN12101643), having been ethically approved by two Institutional Committees (University Hospital of Patras, Greece and Queen Margaret University Edinburgh, UK (7052/4-7-2011)).

Allocation of participants to the two groups was concealed to participants and investigators by means of an independent confidential assignment (concealed coded listing, maintained until after data analyses). A total of 10 blocks of five patients were randomly assigned to the two groups using a computer-generated number sequence overseen by an independent statistician. Groups were subsequently augmented by two patients presenting for surgery immediately prior to the study's deadline for recruitment and assigned in the original block-allocation order, leading to a total of 52 patients in the study.

Participants

In all, 70 consecutive patients (May 2012–May 2014) undergoing primary standardized cemented

unilateral total knee replacement (single surgeon; 15 years experience of knee replacement; 50 knee replacements per annum) were invited to participate in the study. The inclusion criteria for participants were that they had elected to undergo primary unilateral total knee replacement as a result of advanced osteoarthritis and they had been ambulatory at the time of surgery. Patients were excluded from the study if they had the following conditions: (a) neurological conditions; (b) vestibular disorders that might affect balance; (c) other lower extremity orthopaedic problems; and (d) unable to communicate or follow instructions. All the participants gave written informed consent.

Isovolumetric rehabilitative procedures

Participants received a standardized hospital-based post surgery care pathway, initiated with bedside physiotherapy. After discharge, at approximately 2 weeks after surgery (range: 15–20 days), patients performed a 12-week programme of self-managed home-based exercises designed to enhance functional capabilities (modified from Piva et al.¹²; see Supplementary Appendix 1). From week 3 to week 8, patients undertook five exercise sessions per week. Sessions increased progressively in duration from 35 to 45 minutes and involved an increase in the prescribed duration of walking from 10 to 20 minutes. Weeks 9–14 required patients to complete 45-minute sessions of exercise three times per week. Each patient's training programme was prescribed and delivered in a standardized manner using an illustrated guidebook of 14 exercises to regulate exercise-specific dosages. Progression within training involved the exercise intensity being adjusted progressively to calibrate with changes in each patient's capabilities, which were assessed weekly. Clinical oversight, by telephone and within scheduled practical sessions, involved patients freely reporting effusion or discomfort and clarifying the delivery (accuracy, dose or safety) of the self-managed exercises. Patients' compliance with the prescribed intensity, duration and frequency of exercise was verified by 7-day recall activity diaries.

Experimental group: focal sensorimotor training

Patients in the experimental group undertook exactly the same procedures and volume of exercises as had been prescribed for the control group. However, the experimental group undertook exercises that focused predominantly on enhancing sensorimotor function capabilities of patients. The exercises included novel formulations of agility and perturbation training techniques^{5,7,12} and substituted for a proportion of training (50% – 7/14 exercises) within usual practice in order to maintain an isovolumetric comparison of training between the experimental and control groups.

Control group

Usual care exercise sessions involved strengthening, stretching, and task-oriented functional exercises of the lower extremity.^{13,14} Supplementary Appendix 1 offers a detailed description of the programmes of training undertaken by the experimental and control groups.

Outcome measures

Randomly ordered assessments of outcome data were collected at presurgery, at 8 weeks post surgery, and at 14 weeks post surgery. The Timed Up and Go Test was selected as the study's primary outcome measure of functional mobility, while also reflecting participants' neuromuscular capabilities for power, agility, balance, and risk of falls.^{15,16} The test involves patients rising from a chair with armrests, walking 3 m, turning, and walking back to sit down. The Timed Up and Go Test has shown good clinimetric properties (minimum detectable change: 2.49 seconds)¹⁶ and is a time-efficient task that reflects multiple themes of activities of daily living.¹⁷

Single-limb standing to measure sensorimotor function was assessed in the operated and non-operated legs using the protocol described by Cachupe et al.¹⁸ A Biodex Stability System (Biodex Medical Systems, Shirley, NY, USA; platform deflection: 12) was used with feedback limited to

an eye-level visual target during concurrent platform tilting over anterior-posterior and mediolateral axes.

Sensorimotor function was also evaluated by knee joint positional error using a passive-active angle reproduction test (tibial bubble inclinometer (Fabrication Enterprises, Inc., USA)) conducted at 25° and 60° of knee flexion and described in detail elsewhere.¹⁹⁻²¹ Joint position error was recorded as the mean angular discrepancy from the target during three replicates at each of the two target knee angles, performed in random order (six trials, 15 seconds inter-trial recovery), using the following expression (absolute values of estimated errors were used for analysis):

$$\text{Joint position error} = \frac{\text{absolute} \\ (\text{trial knee angle} - \text{target knee angle})}{\text{target knee angle}} \times 100\%$$

Patient-reported functional balance capabilities were assessed by the number of falls experienced in the year immediately prior to surgery and during the study's follow-up period. Self-reported functional performance was assessed using the Knee Outcome Survey Activities of Daily Living Scale (minimal detectable change=12.5-17.2 scale units).²² Pain was assessed by a Visual Analogue Scale (minimal detectable change=1.1 cm).²³

Statistical analysis

The effects of the focal sensorimotor exercise training were assessed for each outcome measure using separate factorial analyses of variance (ANOVAs) involving group (experimental; control) by leg (non-operated and operated) and by test occasion (presurgery, 8 weeks post surgery, and 14 weeks post surgery) comparisons, with repeated measures on the latter two factors. Assumptions underpinning the use of ANOVA were assessed and corrections used (Greenhouse-Geisser (GG)) where appropriate. For outcomes that had focused on bilateral limb capabilities (such as the Timed Up and Go), group (experimental; control) and by test occasion (presurgery, 8 weeks post surgery, and 14 weeks post surgery), interactions were assessed

using ANOVA with repeated measures on the latter factor.

Effect size (ES; Cohen's *d*) was calculated using pooled standard deviations.²⁴ A sample size of 30 participants per group was computed to achieve an experimental design sensitivity of 0.80 for the primary outcome of the Timed Up and Go Test (Type I and Type II error rates, 0.05 and 0.20, respectively) in discriminating a moderate relative ES²⁵ between the performance of the groups at the study's primary end-point (14 weeks post surgery). Statistical significance was accepted at $P < 0.05$. Analyses used the Statistical Package for Social Sciences (SPSS; v. 16.0).

Results

Results for 51 of the 52 participants completing the study are reported (the exclusion of one patient was due to the non-completion of an assessment at 14 weeks). The study's CONSORT flow chart and group mean scores at baseline for experimental and control groups, which were statistically similar ($P > 0.05$), are shown in Figure 1 and Table 1, respectively.

The experimental group yielded superior gains in functional mobility and sensorimotor function and in most other outcomes compared to control. These gains for the experimental group ranged between 20% for the Timed Up and Go Test ($P < 0.001$) and 125% for self-reported performance scores (Knee Outcome Survey Activities of Daily Living Scale; $P < 0.001$) by the end of training. Table 2 shows group mean scores for experimental and control groups at baseline, 8 weeks post surgery, and 14 weeks post surgery. Comparisons using *a priori* orthogonal difference contrasts suggested that the superior gains made by the experimental group for the Timed Up and Go Test were elicited progressively over the period of training, with gains elicited between baseline and 8 weeks post surgery (29.1%) and between 8 and 14 weeks post surgery (34.2%). These were similar in magnitude, but significantly greater than control ($F_{1,49} > 11.1$; $P < 0.001$; Table 2).

Figure 2 shows individual improvement scores during the period of training exceeding the minimum detectable change criterion for the Timed Up

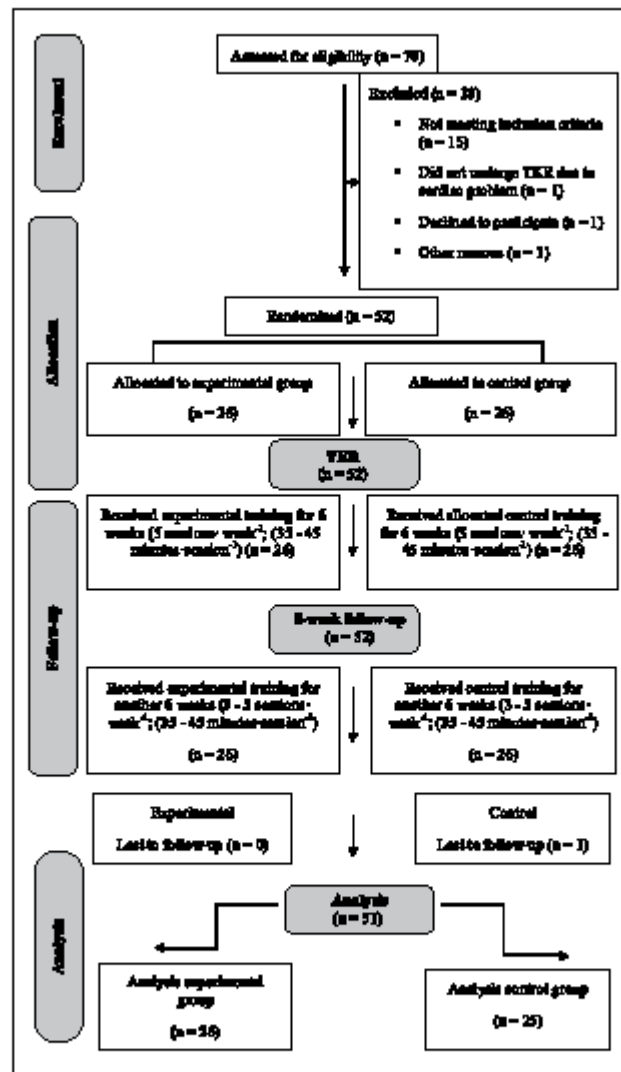


Figure 1. Patient CONSORT flow of the study.
TKR, total knee replacement.

Table 1. Presurgery (baseline) demographic characteristics, time on waiting list, and measures of functional performance and pain.

Variable	Group (mean (SD))	
	Control (n=25)	Experimental (n=26)
Age (years)	72.3 (5.6)	71.3 (5.3)
Height (m)	1.64 (0.10)	1.66 (0.10)
Weight (kg)	82.1 (10.3)	82.5 (8.9)
Time to surgery (weeks)	17.2 (14.9)	15.3 (12.8)
Falls (no. of falls during one year presurgery)	2.4 (0.8)	1.9 (0.6)
TUG (s)	16.9 (3.8)	15.9 (3.6)
VAS (cm)	7.0 (1.1)	6.7 (1.2)

TUG, Timed Up and Go Test; VAS, Visual Analogue Scale.

Table 2. Group mean scores at presurgery and 8 and 14 weeks post surgery.

Variable	Group	Presurgery	8 weeks post surgery	14 weeks post surgery	P-value	F	ES
		Mean (SD)	Mean (SD)	Mean (SD)			
TUG (s)	Experimental	15.8 (3.5)	11.2 (2.9)	8.1 (1.7)	0.002	11.2	2.8
	Control	17.0 (3.7)	15.1 (3.8)	12.4 (2.5)			
VAS (cm)	Experimental	6.7 (1.1)	3.0 (1.3)	0.7 (0.7)	0.001	7.0	6.5
	Control	7.0 (1.1)	4.1 (1.4)	2.4 (0.8)			
KOS-ADL	Experimental	35.4 (6.9)	56.2 (11.4)	79.6 (9.0)	0.001	19.0	5.5
	Control	34.0 (7.3)	50.3 (9.4)	60.6 (9.3)			
OSI (°)	Experimental	3.8 (1.3)	2.7 (0.9)	1.9 (0.6)	0.001	24.8	1.3
	Control	3.4 (1.7)	3.3 (1.4)	3.0 (1.2)			
APSI (°)	Experimental	3.0 (1.4)	2.0 (0.8)	1.5 (0.7)	0.001	16.2	1.4
	Control	2.2 (1.1)	2.0 (0.6)	2.1 (1.0)			
MLSI (°)	Experimental	2.1 (1.0)	1.5 (0.6)	1.0 (0.5)	0.001	21.6	1.3
	Control	2.0 (1.3)	1.4 (0.6)	2.0 (0.9)			
JPE ₃₀ (%)	Experimental	16.3 (6.1)	7.1 (4.1)	5.2 (2.6)	0.001	9.6	1.8
	Control	17.1 (9.6)	13.9 (6.6)	12.8 (5.9)			

P-value signifies the statistical significance of the interaction between the groups over time; ES signifies the absolute difference in outcome measures for each group within the follow-up period (presurgery to 14 weeks post surgery).

TUG, Timed Up and Go Test; VAS, Visual Analogue Scale; KOS-ADL, Knee Outcome Survey Activities of Daily Living Scale; OSI, Overall Stability Index; APSI, anteroposterior Index; MLSI, mediolateral stability Index; JPE, joint position error.

and Go Test (2.49 seconds)¹⁶ for patients in the experimental and control groups.

The experimental group showed 40% greater improvement on the overall stability index compared to control ($F_{2,98}=24.8$; $P<0.001$; Table 2). The operated and non-operated legs showed equivalent patterns of improvement during training. The gains in the overall stability index for the experimental group

between baseline and 8 weeks post surgery and between 8 and 14 weeks post surgery were equivalent, suggesting a superior (compared to control) but progressive response to training ($F_{1,48}>20.5$; $P<0.001$; Table 2).

Training-related improvements in joint position error were similarly superior for the experimental group compared to control at both target angles

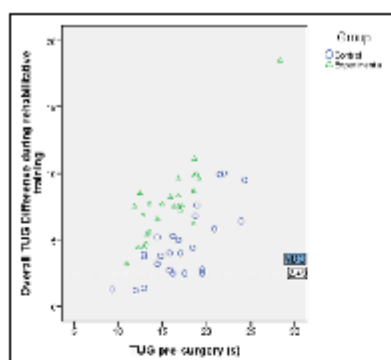


Figure 2. Individual patient's improvement scores during the period of training exceeding the minimum detectable change in functional mobility as assessed by the Timed Up and Go Test. MDC, minimal detectable change; TUG, Timed Up and Go Test; TKR, total knee replacement.

(25° and 60°) and marginally greater for the operated compared to the non-operated leg at 25° of knee flexion ($F_{1,4,70,6GG}=4.3$; $P<0.05$; Figure 3), but not at 60° ($F_{1,6,79,4GG}=9.6$; $P<0.001$; Table 2).

A similar pattern of gains favouring the experimental group compared to control group was shown for pain ($F_{2,38}=7.0$; $P<0.001$; Table 2). Patients' compliance to exercise training showed an ~10% difference in favour of the experimental group.

Discussion

The principal finding of this study was that patients undergoing total knee replacement and initiating self-managed, focal sensorimotor rehabilitative exercise training soon after surgery demonstrated superior gains in functional mobility and sensorimotor function compared to those who performed the functional exercise training.

As it had been expected, this finding offers confirmation that when compared to usual practice, a greater proportion of exercises focusing on improving sensorimotor function within a volume-matched prescription of rehabilitative exercises

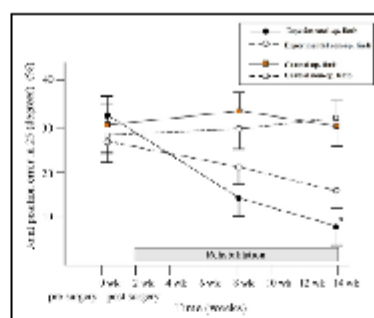


Figure 3. Group mean (SD) scores from presurgery to 8 and 14 weeks following total knee replacement surgery for JPE (%) at 25° of knee flexion of both the operated and non-operated legs for patients undertaking rehabilitation involving focal sensorimotor (experimental) and functional exercise training (control). (Data represent mean \pm SD; * $P<0.05$.) JPE, joint position error; wk, weeks; op., operated.

elicited greater efficacy and gains that are likely to be clinically important.^{16,22,23} The early initiation and self-management of the novel formulations of rehabilitative exercises were tolerated well by patients.

The clinical efficacy of studies incorporating sensorimotor training within the rehabilitation programme of patients undergoing knee replacement has been tentatively endorsed in a recent systematic review.⁴ However, most studies relied on additional volumes (in terms of time-duration) of sensorimotor training on top of the usual practice to deliver effectiveness, thus hindering the ability to attribute gains solely to the focal sensorimotor training.

The isovolumetric delivery of focal sensorimotor and functional exercise training in this study suggest that the superior gains in pain reduction in former studies,^{12,26} together with functional mobility and balance (including an ~50% gain in single limb standing balance), can be attributed to the particular characteristics of exercises promoting improvements in sensorimotor function and not to the effects of a substantially increased volume of sensorimotor training.

Focal sensorimotor exercise training used in this study produced greater gains (~50%) in objective measures of functional mobility (Timed Up and Go Test) compared to those noted (~25%) in studies with similar conceptual designs.⁴ It is plausible that the superior gains would be attributable to the early initiation of sensorimotor exercise training at 2–3 weeks after surgery in this study, increasing the potential for functional recovery compared to delayed initiation observed typically elsewhere (two months post surgery⁴). Furthermore, peak gains in performance were achieved at the end of training for both types of training, and these gains had occurred progressively over the 14 weeks of monitored rehabilitation (i.e. similar training-related effects between presurgery and 8 weeks post surgery and between 8 and 14 weeks post surgery). As a result, the study's findings suggest that there would be no particular efficacy-related advantage in a cessation of exercise training early, as gains were still being accrued at 14 weeks after surgery. Interestingly, Pohl et al.²⁷ had been unable to detect significant gains in proprioception performance after implementing short duration (3-week) sensorimotor training in patients undergoing both knee and hip replacement surgeries. So, it is not unreasonable to assume a strong link between longer duration rehabilitation programmes and good functional and/or sensorimotor outcomes.

Superior gains in sensorimotor function as measured by joint position sense were shown for the experimental compared to the control group at 25° of knee flexion for the operated leg. The experimental intervention assessed in this study had substituted a volume-matched novel formulation of sensorimotor stimuli for conventional exercises used in contemporary practice. Instead of focusing on the use of elastic bands or weights for muscle strengthening (conventional practice), patients in this study were challenged with managing increasing intensity in the use of the whole body, including segmental-mass-related inertia and momentum changes during activities such as step-ups, squats, lateral steps, and obstacle avoidance. Patients were also challenged with progressively increasing levels of vertical ground reaction forces,²⁸ postural balance,²⁹ and by multidirectional force stimuli.³⁰

It is likely that these features facilitated greater gains in sensorimotor function. Indeed, functional re-organization in sensorimotor brain regions has been observed via training strategies that stimulate the neuromuscular system and can potentially lead to the acquisition of improved motor control according to the task demands.³¹

The combination of superior gains in sensorimotor function associated with undertaking focal sensorimotor exercise training was accompanied by a reduction in the incidence frequency of falls ($\chi^2_{(2)}; P < 0.001$). In the year prior to surgery, all patients had reported at least one fall. After surgery, however, whereas 22 patients (~43% of the total sample) within the control group experienced falling during the follow-up period, only 3 patients (~6%) undertaking enhanced sensorimotor exercise training reported a fall. Future studies involving sensorimotor training interventions focusing specifically on the incidence of falls following total knee replacement will be able to corroborate these observations. Nevertheless, the favourable change to the frequency of falling associated with focal sensorimotor exercise training may have been driven by the patients' improvement in functional mobility, with Timed Up and Go Test scores at the end of the study (8.1 ± 1.7 seconds) firmly exceeding a minimally important clinical criterion (13.5 seconds) for critical progressions in the risk of falls.^{32,33} Further corroborating evidence for the superiority of the experimental group in contrast to the control group was that all participants exceeded the minimum detectable change (2.49 seconds) for the Timed Up and Go Test.¹⁶

The experimental group elicited a significantly superior reduction in the patients' perceptions of pain (Visual Analogue Scale) compared to the control group. The extent of the reduction (89%; 6.0 cm) for focal training in particular substantially exceeds that noted for studies with a similar conceptual design⁴ to that of the current one (33%–42%; ~1 cm). As such, the findings suggest that the characteristics of exercises within the focal sensorimotor training as well as the early initiation after surgery are potentially important features underpinning the favourable improvements in the patients' perceptions of pain.

Overall, the results from this study suggest that enhanced efficacy for sensorimotor exercise training can be achieved by patients self-managing rehabilitation. Early post-surgery initiation of a reasonable volume of exercise training (three to five sessions per week; 35–45 minutes per session; 12-week programme) incorporating focal exercise stimuli from the beginning of the training programme as integral components of it (and for them not to be added later as extra features to contemporary functional exercise programmes) improved functional mobility and sensorimotor function. Conclusions within the recent systematic review⁴ might usefully be modified to take account of this emerging evidence for optimized timing and volume of sensorimotor exercise training for patients electing total knee replacement surgery.

Limitations to this study were related to its design and delivery. Patients' compliance with exercise training was monitored by self-reported diaries rather than by direct evaluation, which may have led to increased heterogeneity among patients' dose-responses. Progression within training was monitored and evolved according to patients' weekly functional and postural control capabilities but not titrated against specific objectively measured criteria or milestones. This feature of this study may have hindered the efficacy of its rehabilitative interventions. Nevertheless, this study employed a modestly sized sample of participants undergoing surgery for total knee replacement, which precludes excessive generalization of the study's findings.

In summary, patients initiating a novel formulation of self-managed, focal sensorimotor rehabilitative exercise training soon after total knee replacement showed superior gains in functional mobility and sensorimotor function compared to contemporary practice. The novel exercise programme was delivered successfully using home-based care and involved an increased proportion of exercises focusing on improving sensorimotor function integrated within a volume-matched prescription of rehabilitative exercises. This study's findings facilitate informed decision-making within clinical practice and promote the effective use of focal sensorimotor exercise training.

Clinical message

- Focal sensorimotor rehabilitative training implemented early after surgery within a self-managed, home-based environment is more beneficial than functional exercise training for enhancing functional mobility and sensorimotor function in patients following total knee replacement.

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Supplement material

Supplementary material is available for this article online.

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